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In addition, annual reports from various hospitals, numerous contributions to discussions, and newspaper articles.

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Kaposi's Varicelliform Eruptions[1]

by

INGVAR ALM

Ever since the clinical picture of Kaposi's varicelliform eruptions was first described (4), discussion has been concerned mainly with the question of whether the aetiologic factor is a bacterial infection, particularly by staphylococci, or whether the disease is caused by some filtrable virus. With the improvements in the methods of specifying the latter organisms, the virus has entered into the foreground of the discussion. Since 1941 a number of workers, particularly in America (1, 2, 3, 5, 7, 8, 9), have succeeded in isolating the herpes virus from the vesicles and have also demonstrated antibodies with a specific effect against it in the patients. Little interest has been accorded in these investigations to the rôle played by bacteria, particularly the staphylococci, even though in many cases it has been stated that staphylococci and at times streptococci could be grown from the contents of the vesicles.

Between 1940 and 1947 a total of five cases of this disease in infants has been reported from the Norrtull Hospital and the Sachs Children's Hospital.

Clinical Observations

The three earlier cases, in which the general condition was considerably affected, had previously suffered from eczema, and the onset of the disease was acute, with high fever and umbilicated vesicles in the eczema. This was interpreted as a virus infection

[1] Lecture given at a meeting of the Swedish Medical Association, Section for Paediatrics and School Hygiene, on March 23, 1948.

Table 1. The most

Case No.	I	II
Hospital	Norrtull	Norrtull
Record No.	418/1940	327/1942
Month	June	March
Age	6 mo.	7 mo.
Sex	Male	Male
Weight at Birth	3 800 g	3 360 g
Weight on Admission	6 950 g	9 020 g
Feeding	Breast milk	Breast milk 5 mo. Mixed feeding.
Heredity — Eczema	Brother eczema as child.	0
Heredity — Asthma	0	0
Eczema — Age at Onset	1 mo.	2 mo.
Eczema — Localization	Face	Face, arms, and legs.
Known Contact With Vaccinia	0	0
MSR on Admission	27 mm/1 hr.	47 mm/1 hr.
WBC		
Min. and Max.	11 400	5 400
During 1st Week	12 200	8 000
Size of Umbilicated Vesicles	»Small vesicles»	»Up to confetti.»
Virologic Investigation	—	—
Bacteriological Investigation	—	—
Subsequent Bacteriolytic Titer	—	—
Therapy	1 sulfa prep. 3 blood injec.	2 sulfa prep.
Stay in Hospital Until Afebrile	3 wks.	3 wks.
Final Results	Cured	Cured

together with a secondary infection. Vaccine virus was suspected in all three cases, but no vaccinia could be demonstrated in any instance. No virological nor bacteriological studies were made.

important clinical data.

III	IV	V
Sachs	Norrtull	Sachs
80/1943	164/1946	1009/1947
Jan.	March	Dec.
5 mo.	9 mo.	5 mo.
Male	Female	Male
3 910 g	3 800 g	3 810 g
7 550 g	9 400 g	6 700 g
Breast milk	Breast milk 3 1/2 mo. Mixed feeding.	Breast milk + suppl. feedings. Mixed feeding.
Sister eczema as child.	0	Father, mother, brother eczema in childhood.
0	Father, sister bronchitic asthma.	0
1 mo.	2 mo.	3 wks.
Face	Face, hands.	Face, arms, hands, chest.
0	0	0
16 mm/1 hr.	17 mm/1 hr.	30 mm/1 hr.
5 500 9 500	2 100 14 300	7 400 16 500
»Up to size of a pea.»	»Up to confetti.»	»Size of hemp-seed.»
—	Paul's test neg.	—
—	β-streptococci. Staph. aureus.	β- and γ-streptococci. Staph. aureus.
—	Antistreptolysin titer normal: 40 U/ml.	Antistaphylolysin titer very high: 12.5 U/ml.
2 sulfa prep. 3 blood injec. 1 blood transfusion.	1 sulfa prep. Penicillin. 1 blood transfusion.	1 sulfa prep. Penicillin. Streptomycin.
3 1/2 wks.	8 days	4 days
Cured	Cured	Cured

The fever lasted for three to four weeks and neither therapy with different sulfonamides and various antibacterial ointments applied locally nor injections of blood had any demonstrable effect.

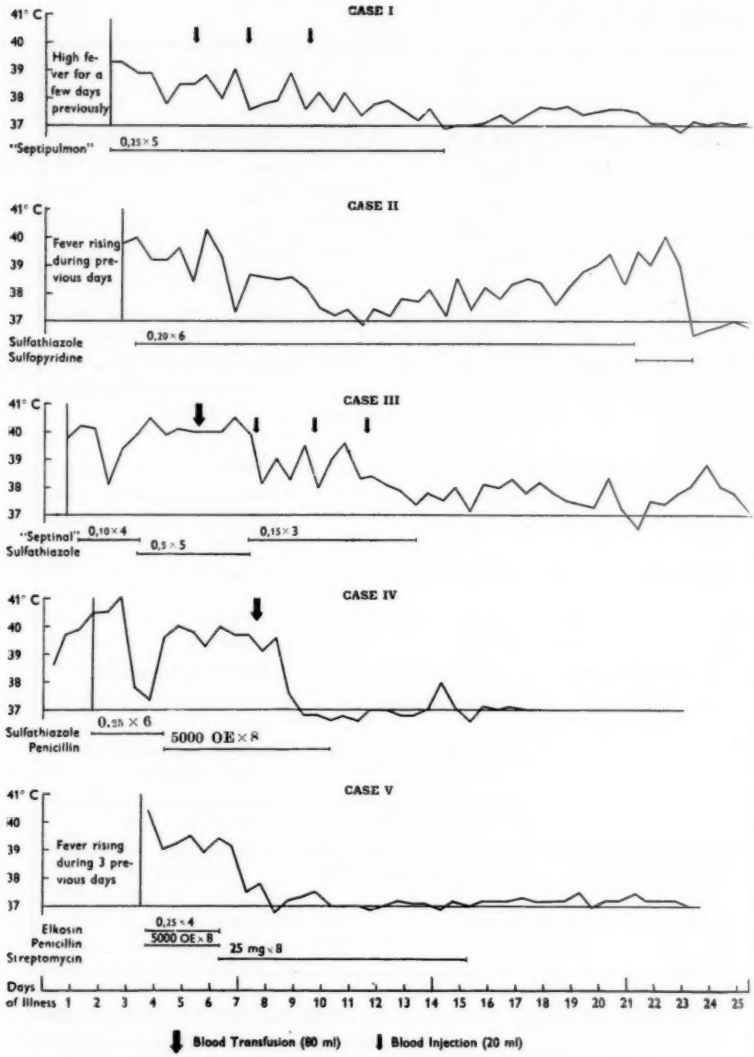

Fig. 1. Temperature curves in all 5 cases.

Fig. 2. Case IV on admission to hospital.

Case IV. Inoculation of the vesicular content on the cornea of rabbits gave negative results. β-streptococci and haemolytic Staph. aureus were demonstrated bacteriologically. The anti-streptolysin titer was investigated in the later stages and showed normal values of < 40 U/ml. Sulfathiazole and penicillin therapy had no noticeable effect. Ten days after the onset there was a critical fall in temperature. 80 ml of blood given as a transfusion on the previous day may possibly have contributed to the fall in temperature, although a transfusion of the same quantity was given in Case III without any effect on the temperature curve.

Case V. The patient had been hospitalized three weeks previously for eczema, at which time α-streptococci and Staph. aureus were present in cultures from the fauces. He was readmitted with a high fever and a typical picture of Kaposi's eruption with umbilicated vesicles and 7 400 WBC. Cultures from the vesicular contents showed the presence of β- and γ-streptococci and Staph. aureus. Penicillin and Elkosin were immediately prescribed and

resistance determinations to Elkosin, penicillin, and streptomycin were made on these bacteria. The streptococci proved to be penicillin-sensitive but Elkosin- and streptomycin-resistant. The Staphylococci were, however, sensitive to streptomycin only and resistant to Elkosin and penicillin. Since there was no fall in temperature after three days despite the therapy, a change was made to streptomycin. This was followed by a fall in temperature within twenty four hours. The fact that Staphylococci had contributed to the disease was shown by the fact that the antistaphylolysin titer, determined two weeks later, was 12.5 U/ml. The normal value for comparable healthy subjects from the Sachs Children's Hospital was 0.6—1 U/ml (6). The figure found in the case reported was thus undoubtedly pathologically increased.

Summary

An account is given of the symptomatology and therapy in five cases of Kaposi's varicelliform eruptions in infants between the ages of five and nine months. In one case bacteriologic and serologic studies showed the presence of Staphylococci, and resistance determinations showed that these bacteria were sensitive only to streptomycin. The patient rapidly became afebrile and there was a considerable improvement in his condition after administration of this drug.

Résumé

Eruptions varicelliformes de Kaposi.

On relate la symptomatologie et la thérapeutique mise en oeuvre dans cinq cas d'éruptions varicelliformes de Kaposi, chez des enfants de 5 à 9 mois. Dans un de ces cas, les études bactériologiques et sérologiques montrèrent la présence de staphylocoques, et les déterminations de résistance montrèrent que ces bactéries n'étaient sensibles qu'à la streptomycine. Le patient devint rapidement afébrile, et il y eut une amélioration considérable de son état après administration de ce produit.

Zusammenfassung

Kaposi's varicelliförmige Ausschläge.

Eine Darstellung der Symptomatologie und Therapie von fünf Fällen an Kaposi's varicellenförmigen Ausschlägen bei Säuglingen im Alter von 5—9 Monaten wird gegeben. In einem Fall zeigten die bakteriologischen und serologischen Untersuchungen das Vorhandensein von Staphylokokken. Bestimmungen der Resistenz zeigten, dass diese Bakterien nur auf Streptomycin empfindlich waren. Der Patient wurde sehr bald fieberfrei und nach Verabreichung dieser Medizin konnte man eine bedeutende Besserung in seinem Befinden konstatieren.

Sumario

Erupción variceliforme de Kaposi.

Se describe la sintomatologia y terapeutica de 5 casos de Erupción variceliforme de Kaposi en niños de 5 a 9 meses.

En un caso el estudio bacteriológico y serológico demostró la presencia de estafilococos, y las determinaciones de resistencia demostraron que estas bacterias eran solamente sensibles a la Estreptomicina. El enfermo, luego de la administración de esta droga se vuelve afebril y se comprueba una mejoria considerable de su condición.

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FROM QUEEN LOUISE'S CHILDREN'S HOSPITAL, COPENHAGEN.

On Somatic Disorders as Causes of Behaviour Difficulties

by

OLUF ANDERSEN, M.D.

When considering a child with behaviour difficulties and neuroses, the attitude of the modern doctor and psychologist usually leads him to turn his attention primarily to the environment as a possible cause of the child's symptoms.

Environmental harm is so frequently assumed that the part played by the patient's own physical and mental constitution in the development of nervous disorders tends to be forgotten.

It is, however, just as important to investigate a child's physical condition as his environment. To concentrate on only the one is to do merely half of the job and may have serious consequences for the child. It should also be noted that the child's closest environment is intimately related to his own constitution. Thus an environment which must be considered unfavourable is sometimes found to be so because the mental constitution of the parents is one which may be described as psycholabile. The child of such parents may, quite naturally, be born with a psycholabile constitution and thus be more difficult to manage than an average child. This circumstance works back in its turn on the psycholabile parents, who become still more inconsistent and nervous with the child than they would be if they had a child with a more stable mental constitution. In other words, *the child is certainly affected by its environment, but the environment is also affected by the child.* In this way the child's own mental constitution plays a large part. This must not be forgotten when one is dealing with a child who is suffering from his environment.

Similarly, the child's physical condition is of some significance both in his reaction to his environment and in its reaction to him.

If a child is physically weakened by illness, his mental condition is also affected. Even quite ordinary illnesses, such as colds, anaemia, or perhaps bad living habits such as too little sleep can make a child irritable and difficult to deal with. These conditions may work on the parents and make them behave badly to the child, since the cause of his behaviour is not understood. In other words, the environment becomes unsuitable.

If these children are studied only from the psychological and psychiatric aspects, they will readily be put down as children suffering from their environments; this is, indeed, not actually wrong, since the environment is also at fault, but here the environment is less significant. The important thing is to discover the underlying physical disorder. Two case histories will illustrate this.

Case 1. 942/48. K.W., a boy aged nine years, was the second of three siblings. He was admitted to Queen Louise's Children's Hospital because of headaches. There was nothing of interest in his history apart from the following.

The headaches began after he began to go to school; they came on particularly when he was tired, but now and again after quarrels with his playmates. He had difficulty in keeping up with school work and was transferred to a special class. His mother said that he was nervous and sensitive and cried easily. Soon after he began school he had a concussion from a fall in the school yard; he lost consciousness, vomited, and had to be kept in bed for eight days, after which he was symptom-free and returned to school.

In conclusion it was said that he snored, but he had no tendency to catch cold. Examination showed a boy of normal physical development; the adenoids were enlarged, the tonsils were fairly large, and there were some palpable glands in the neck. Otherwise no abnormality was found on general physical examination. The haemoglobin was 93 %; tuberculin patch and Mantoux tests were negative; and the W.R. was negative.

Thus this was a boy who had had headaches for about two years after beginning school. The headaches could be directly related to a concussion and to difficulties at home and at school.

It seemed, however, that consequences of the concussion could be excluded, both on account of normal radiography of the skull and ophthalmoscopic and neurological findings and because the boy was symptom-free in the first period after recovering from the injury.

Both psychological and psychiatric examinations showed that his I.Q. was 94. He was in conflict with his mother and his little sister, who

occupied too central a position in the family. Also, he was teased a good deal by his schoolmates and had difficulty in keeping up with the schoolwork, so that he was transferred to a special class.

He gave the impression of being very restrained and emotionally suppressed. He seemed to be just the type which reacts to mental strain with physical symptoms. The general impression was that there was sufficient conflict, both at home and at school, to explain the condition.

The remaining investigations, however, showed quite otherwise. As already mentioned, he had enlarged adenoids; the sedimention rate was found to be raised to 31 mm per hr. The antistreptolysin titer was 280 and microscopi of the urine finally showed red blood corpuscles, without other cells or casts. There was no albuminuria and culture of the urine was sterile. Diuresis, specific gravity and kidney function tests, and urography were all normal.

Thus the boy had an adenoiditis, cervical adenitis, a raised sedimentation rate, and latent nephropathy. He was given a course of penicillin, after which his adenoids were removed. After this, the haematuria disappeared, the sedimentation rate returned to normal, and the AST fell. The patient has been symptom-free ever since. It is probable that the headaches were due to a chronic infection in the nasopharynx. In these circumstances, it is not surprising that the child was tired and indisposed and had difficulty in adapting himself to his surroundings.

One cannot, however, quite ignore the possibility that his mental troubles were related to his difficulties at school.

Case 2. 22/49. O.B., a boy aged nine years, was admitted to Queen Louise's Children's Hospital because of headaches. Had been admitted previously when three and a half years old for behaviour difficulties and enlarged adenoids and was at that time thought to be suffering from his environment. Nothing else significant was noted; the urine was normal at that time. Treatment consisted of removal of adenoids and advice to the parents.

Later, he was brought to a psychiatric clinic, where a kindergarten was recommended until he reached school age. He remained, however, difficult, being very unbalanced at home, with occasional paroxysms of rage. The mother expressed it as her opinion that »he had nerves». She was said by the doctor to be nagging and dominating. The boy was apparently better at school than at home. He was now admitted for further investigation because in recent years he had had attacks of headache. General examination revealed nothing abnormal. At first one was inclined to believe that the headache was psychic and related to the behaviour difficulties. Ophthalmoscopy, radiography of the skull, examination of the cerebrospinal fluid, and neurological examination showed normal findings. The W.R. was negative.

Hypoplasia of the right kidney as a result of chronic pyelonephritis.

However, a series of other examinations showed that the diagnosis of psychogenic headache had to be abandoned. The blood pressure was consistently raised, the systolic pressure varying between 130 and 145 while the diastolic pressure varied at about 100. There was no albumen or sugar in the urine and microscopy showed only occasionally 2—3 lycocytes; otherwise there was nothing abnormal. Culture of the urine was negative.

The different kidney tests showed normal function. Diuresis and specific gravity were normal. Indirect urography showed a small filling of the right renal pelvis: compared with the well-filled pelvis on the left side it might be called hypoplastic. The left kidney shadow appeared to be slightly larger than normal. (— See figure.)

A right nephrosclerotic kidney (with compensatory enlargement of the left kidney) was diagnosed. A nephrectomy was carried out on the right side. Pathological examination of the removed kidney showed chronic pyelonephritis.

After the operation the blood pressure fell to normal (systolic 105, diastolic 65). Kidney function tests after the operation showed normal function and the patient has since been symptom-free.

In this case it is reasonable to assume that the boy's headache and behaviour can be explained as results of the chronic renal lesion. The condition of the removed kidney suggests that the renal condition had been present for years — how long one cannot say, since he never showed any signs which could suggest an affection of the urinary tract. The fact that no abnormality was found in the urine when he was in hospital at the age of three and a half years does not imply that the kidney could not have been affected even at that age. At his last admission there were no abnormal constituents in the urine in spite of confirmed chronic pyelonephritis.

It seems reasonable to assume that at least a fair part of the boy's behaviour difficulties can be attributed to the fact that he was not well.

These case histories show how careful one must be in judging the mental symptoms of children. One must always bear in mind that children with even minor lesions easily become irritable and unbalanced and show behaviour difficulties. Therefore, in all cases where these occur, one must make sure that the child is healthy before accepting environmental conditions as the cause.

It must be emphasized that when dealing with a child suffering from its environment there should be close cooperation between the psychiatrist, psychologist, and paediatrician, and no such child should have psychological or psychiatric examination before a thorough examination has established that he is healthy.

Summary

The author points out the effects that somatic disease in children may have on their behaviour and presents two cases.

A boy of nine years with headache and behaviour problems improved after an adenoidectomy for chronic upper respiratory infection. The second case, a boy of nine years who also had headache and psychological difficulty, proved to be a case of renal hypoplasia with hypertension.

The author stresses how carefully the mental symptoms of children must be assessed, pointing out that children with even minor somatic lesions easily become irritable and unbalanced.

Therefore it is necessary to examine children with behaviour difficulties thoroughly, taking somatic diseases into consideration, before one accepts the diagnosis of environmental difficulties.

Résumé

L'auteur décrit les effets que la maladie somatique des enfants produit sur leur comportement, et présente deux cas: un garçon de 9 ans, sujet à des maux de tête, et à des problèmes de comportement améliorés par suite de l'ablation des glandes adénoïdes pour infection chronique des voies respiratoires supérieures; le second cas, un garçon de 9 ans, également sujet à des maux de tête et à un malaise psychologique qui se sont révélés être un cas d'hypoplasie rénale avec hypertension.

Il souligne que les symptômes mentaux des enfants doivent être soigneusement établis, en montrant que des enfants présentant des lésions somatiques mineures deviennent facilement irritables et maladaptés. C'est pourquoi il est nécessaire d'examiner minutieusement les enfants présentant des malaises de comportement, en prenant en considération les maladies somatiques avant que l'on soit satisfait du diagnostic des malaises environnants.

Zusammenfassung

Der Verfasser legt die Wirkungen dar, die somatische Krankheiten bei Kindern haben können bezüglich ihres Verhaltens, und stellt zwei Fälle vor.

Ein Knabe von 9 Jahren mit Kopfschmerz und Anpassungsschwierigkeiten; Besserung nach Adenoidektomie wegen chronischer Infektion der oberen Luftwege. Zweitens ein Knabe von 9 Jahren, ebenfalls mit Kopfschmerzen und psychischen Schwierigkeiten. Der Fall erwies sich als ein solcher von renaler Hypoplasie mit Hypertension.

Der Verfasser betont wie sorgfältig die mentalen Symptome bei Kindern beachtet werden müssen, und legt dar, dass Kinder

auch mit geringeren körperlichen Schädigungen leicht reizbar werden und das Gleichgewicht verlieren.

Daher ist es notwendig, Kinder mit Schwierigkeiten gründlich zu untersuchen, also körperliche Krankheiten in Betracht zu ziehen, statt sich zu begnügen mit der Feststellung von Milieuschädigungen.

Sumario

El autor recalca los efectos que la enfermedad somática puede tener sobre el porte de niños y presenta dos casos.

El primero es de un muchacho de 9 años con dolor de cabeza y problemas de porte, el cual mejoró después de adenoidectomía para infección crónica perteneciente a la respiración superior. El segundo caso es de un muchacho de 9 anos también con dolor de cabeza y dificultad psíquica, quien resultó ser un caso de hipoplasia renal con hipertensión.

Se recalca cuán esmeradamente se deben fijar los síntomas mentales de niños y se subraya que los niños aún con menores lesiones somáticas se vuelven fácilmente irritables y desequilibrados.

Por esta razón es necesario examinar esmeradamente a los niños que tengan dificultades de porte, tomando en consideración las enfermedades somáticas antes de contentarse con las dificultades diagnosticadas de ambiente.

FROM THE PAEDIATRIC CLINICS AT KRONPRINSESSAN LOVISA'S CHILDREN'S HOSPITAL AND THE NORRTULL HOSPITAL, STOCKHOLM.
(CHIEFS: PROFESSORS A. LICHTENSTEIN AND A. WALLGREN.)

The Electroencephalogram in Congenital Hypothyreosis

by

M. D'AVIGNON and K.-A. MELIN

Upon examination of a relatively large number of congenital hypothyreosis cases, one finds that after adequate treatment many develop in a completely normal way. Yet others which were treated equally early and equally rationally sometimes show considerably retarded mental development.

This circumstance has induced the authors to try to determine whether in certain cases there is injury to the central nervous system from the very beginning or whether such injury occurs in the course of development. At present, electroencephalography is probably the method best adapted to an investigation of this type. With the aid of electroencephalography one may, among other things, record the so-called alpha rhythm, the acceleration of which with increasing age is well known (BERNHARD and SKOGLUND 1939, LINDSLEY 1939, HENRY 1944, LARSSON, MELIN, ÖHRBERG, and ÖHRBERG 1949).

Our present object is to follow the new cases of congenital hypothyreosis which receive adequate thyroid medication. Since there are only a few such cases each year, these investigations have as yet only been begun. We have, however, felt it to be of interest also to investigate the available previously treated cases of this disease.

The connection between basal mentabolism and EEG was investigated early (LINDSLEY and RUBINSTEIN 1937). Normal cases treated with thyroxin showed a correlation between a rise in basal metabolism and an increase in the alpha frequency. Administra-

tion of dinitrophenol (HOAGLAND, RUBIN, and CAMERON 1939) appeared to give the same result. It seems that the experiments in question failed to give rise to any other EEG changes, such as dysrhythmia. These conditions seem to be in accord with the findings in pathological conditions. In hypothyreosis the rhythm is slower than normal (BERTRAND, DELAY, GUILLAIN, and GUILLAIN 1938) and in hyperthyreosis more rapid (GIBBS and GIBBS 1941).

In the published investigations of pathological cases there are, however, no comparisons between on the one hand the patients' somatic and psychical development, the institution and the course of treatment and, on the other, the occurrence of EEG changes. Hence we have tried to compare data of this kind in twenty-two cases of congenital hypothyreosis aged three to twenty-seven years. All cases were under the care of the paediatric clinics at Kronprinsessan Lovisa's Children's Hospital, the Norrtull Hospital, and the Samariten Children's Hospital in Stockholm. Congenital hypothyreosis was definitely established during the first year of life in seventeen of these cases, during the second year in four, and during the third in one. In the course of this first stay in the hospital thyroid medication was begun for all and subsequently kept up continuously in every case but one. The result of this treatment was that somatic development was normal in the twenty-one patients who continued treatment without interruption. A single patient, a girl now nine years old who lives in very bad social conditions and has not received treatment continuously, shows distinct signs of cretinism. In 1948 all the patients underwent clinical examinations. They also took Terman-Merrill intelligence tests except in three cases in which Bühler-Hetzer tests were given (Cases 753, 1059, and 1138).

In contrast to the somatic course, the psychical development in these cases was very different (see Table 1).

As the table shows, psychical development as judged by intelligence testing varied widely. Even when therapy was begun very early, the results were sometimes bad (for example, Case 1059). Correspondingly, there were several cases of classic congenital hypothyreosis in which treatment was begun relatively late and yet the final results were good (for example, Case 625).

Table 1

No.	Sex. Age in Yrs.	Therapy Begun at Age (Yrs.)	I.Q.	Verdict	EEG Findings
753	F. 3 1/2	5/12	25	Apathetic, non-educable	Slow (2–4/sec.)
721	F. 3	8/12	c. 25	Probably imbecile	Dysrhythmical large 3/sec. waves
1059	F. 9	6/12	27	Apathetic, non-educable	Slow (4–6/sec.)
237	M. 9 1/2	3/12	60	Apathetic, infantile, unable to concentrate	Slow (6–8/sec.)
956	F. 19	9/12	61	Calm, manually dexterous	9–11/sec. with low amplitude
1038	F. 10	1 3/12	62	Slow, able to concentrate (cretin)	8/sec. together with some 3–5/sec. activity
727	M. 16	2/12	80	Apathetic, unable to concentrate	Normal (9–10/sec.)
1013	M. 4	2/12	81	Calm, able to concentrate	Normal (4–9/sec.)
905	M. 6 1/2	3	88	Slow, unable to concentrate	Markedly dysrhythmical. Large 4–6/sec. waves
990	F. 20	4/12	88	Tense, able to concentrate	Normal (10/sec.)
711	F. 9	2/12	88	Calm, fumbling	Slow (4–6/sec.)
1138	F. 3	1	91	Lively, unable to concentrate	Rapid (8/sec.)
808	M. 5	3/12	92	Lively, able to concentrate	8/sec. and clusters of 3/sec. waves
967	F. 3 1/2	1/12	93	Restless, unable to concentrate	Normal (3–7/sec.)
790	F. 7 1/2	3/12	99	Lively, able to concentrate, defiant	Markedly dysrhythmical (10–11/sec.)
945	M. 13 1/2	1 6/12	99	Lively, able to concentrate, manually dexterous	Normal (9 1/2/sec.)
59	F. 8 1/2	2/12	102	Temperamental, manually dexterous	Normal (7–10/sec.)
1014	M. 11 1/2	4/12	108	Lively, concentrated	Normal (9–10/sec.)
953	F. 3 1/2	1 2/12	109	Lively, manually dexterous	Rapid (9/sec.)
933	F. 27	1 6/12	110	Ambitious, lacking in self-confidence	9–9 1/2/sec. and relatively many 5–8/sec. waves
725	F. 4	1 4/12	110	Lively, able to concentrate	Somewhat slow (3–6/sec.)
625	M. 6	2 2/12	113	Lively, unable to concentrate, manually dexterous	Normal (9 1/2/sec.)

The clinical reports on these patients have now been supplemented by EEG examinations. All of these were carried out in the electroencephalographic laboratory at Kronprinsessan Lovisa's Children's Hospital. A six-channel Grass electroencephalograph, Model III, was used, and in each examination ten silver disc electrodes were applied to the patient's scalp. They were attached with collodium, with a thin layer of electrode jelly between the electrodes and the scalp. The electrodes were applied frontally, parietally, temporally, and occipitally. In addition the ear lobes were used as »indifferent» electrodes. Both unipolar and bipolar leads were taken from all the electrodes. The records were analyzed without knowledge of the psychical status of the patient in question — only the age was known. The different data were not compared until all the material had been collected.

Among the twenty-two patients examined eight showed completely normal EEG's. Those of five deviated from the normal only slightly. Seven had markedly pathological EEG's and two showed unusually rapid activity for their ages.

Most conspicuous among the more pronounced EEG changes was the occurrence of pathologically slow waves, sometimes with a certain increase in amplitude, sometimes grouped in shorter or longer sequences. In all cases the changes were distributed generally. There were no cases of hemisphere asymmetry or focal findings. Upon comparison with normal cases GUILLAIN and his co-workers noted a decrease in amplitude, but we failed to observe this. On the contrary, there was an increase in certain cases. Their cases consisted of untreated cretins, however.

The table shows clearly that four of the seven cases with pathological EEG's were in the poorest psychical condition of all. Two of the remaining three showed psychical defects, although their I.Q.'s were as high as 88. The EEG's of all these patients showed many slow waves for their ages. In the only case in which the EEG was adjudged pathological in a psychically well-developed patient the record was markedly dysrhytmical, but the number of particularly slow waves not especially striking.

The curve of one patient (Case 727) showed normal frequency even though he was apathetic and unable to concentrate and

seemed less intelligent than his I.Q. indicated. A possible explanation is that he had for some time been receiving a comparatively large thyroidea dose which may have speeded up his alpha frequency. In general the thyroidea dose given the patients was regarded, on the basis of their normal somatic development and lack of symptoms of hyperthyroidism, as satisfactory. It was questioned only in the case of the two three year olds who, although without clinical symptoms, showed a rhythm rapid for their age, preponderantly 8—9/sec. activity. The assumption was strengthened further upon repeated examinations of a nine year old girl (Case 59). At three different EEG examinations she showed an alpha frequency of 8—10/sec. As she appeared somewhat overtreated, her thyroidea dose was reduced by half. A further follow-up EEG examination some time later showed that her alpha frequency had sunk to 7—8/sec.

The thyroidea dosage given here probably could otherwise hardly have been capable of affecting the patient's alpha frequency by accident. We have tried to throw light on this by giving six children aged five to fourteen the same proportional thyroidea doses as the hypothyreosis patients. The substance was administered for seven days and EEG's were recorded before the introduction of and in connection with the breaking off of medication. No change whatever in the rhythm could be discerned. In this connection it should be noted that the experimental investigations cited were carried out on normal individuals and using considerably larger doses.

In spite of the fact that our series of cases is still so small that it cannot be treated statistically, the investigations undertaken thus far comparing psychical development with the EEG curves in treated cases of congenital hypothyreosis seem to indicate that in cases with a low I.Q. (60 and under), the EEG is markedly retarted even when these patients receive adequate thyroidea treatment and show normal somatic development. On the other hand, almost all psychically normally developed patients (in this material with an I.Q. above 90) show normal alpha rhythm. In a transitional group the EEG is pathological in two

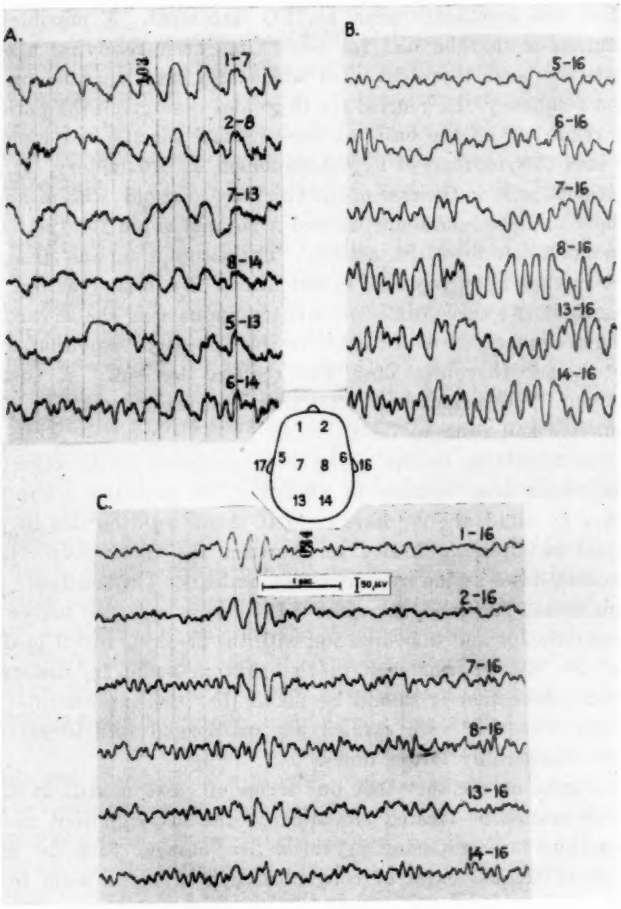

Fig. 1. EEG in some cases of congenital hypothyreosis.
A. Case 237. B. Case 905. C. Case 711.

patients who in spite of an I.Q. of 88 are in some respects mentally underdeveloped.

Thus in summary it may be said that these investigations have shown that there is apparently general brain damage in

mentally underdeveloped patients, insofar as this damage expresses itself in a pathological EEG. When the damage occurred cannot be determined on the basis of this series of cases. Only continuous series investigations of new cases may be expected to throw light on the problem. Perhaps when retardation of the normal increase in the alpha rhythm is discovered at an early stage, it will be possible to counteract the development of central damage by intensifying the thyroid therapy.

Summary

Twenty-two cases of clinically determined congenital hypothyreosis were examined along with a follow-up study by means of electroencephalography. All the patients except one were adequately treated and normally developed somatically, but their mental development showed a wide range of variation. In general, the psychically normally developed patient had an EEG with normal frequencies, while those who were most poorly developed mentally seemed to show general cerebral damage reflected in the form of a pathological EEG. The time at which this injury arose will be the object of further study.

Résumé

Vingt-deux cas d'hypothyréose congénitale diagnostiqués cliniquement furent examinés par une étude suivie au moyen d'électroencephalographie. Tous les patients sauf un furent traité de façon adéquate, et se sont développés physiquement de façon normale, alors que leur développement mental se montrait très différent. En général le patient développé psychiquement de façon normale avait un EEG à fréquences normales, tandis que ceux qui étaient moins bien développés mentalement semblaient présenter des atteintes cérébrales générales se manifestant sous la forme d'un EEG pathologique. L'époque à laquelle ces lésions apparaissent sera l'objet d'études ultérieures.

Zusammenfassung

22 Fälle von angeborener Hypothyreosis wurden klinisch verfolgt und elektroencephalographisch untersucht. Alle diese Patienten ausser einem waren adäquat therapeutisch behandelt und

waren physisch normal entwickelt, ihre geistige Entwicklung zeigte dagegen grosse Differenzen. Im allgemeinen hatten die psychisch normal Entwickelten ein normal Aussehen des Elektroencephalogramms mit normaler Frequenz. Dagegen zeigten die geistig Zurückgebliebenen allgemeine cerebrale Schädigungen in Form eines pathologischen EEG. Der Zeitraum in dem diese cerebralen Schädigungen beginnen soll ein Objekt weiterer Studien sein.

Sumario

22 casos de hipotiroidismo congénito diagnosticados clinicamente, fueron examinados y seguidos con estudios electroencefalograficos. Todos los pacientes con ecepción de uno recibieron el tratamiento adecuado, y alcanzaron un desarrollo somatico normal, pero en su desarrollo psiquico demostraron un margen de variaciones muy amplias. Como regla general al paciente con desarrollo psiquico normal presento un electroencefalograma con frecuencias normales, mientras que los que tenian un desarrollo mental mas insuficiente, parecian mostrar lesiones cerebrales generales, reflejadas en forma de un electroencefalograma patologico. El momento de aparición de estas lesiones, sera objeto de nuevos estudios.

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FROM THE PAEDIATRIC CLINIC, UNIVERSITY OF LUND (CHIEF: PROF. STURE SIWE) AND THE FLENSBURG CHILDREN'S HOSPITAL, MALMÖ (ACTING CHIEF: STEN AXTRUP).

Iso-Immunization in the A B O System and Morbus Haemolyticus Neonatorum

by

STEN AXTRUP

As early as 1923, OTTENBERG suspected that an incompatibility between A B O blood groups of mother and child could cause pathological conditions in the newborn, but he was unable to produce evidence in support of his belief. In 1924 POLAYES AND ASSOCIATES concluded from a study of cord, foetal, and maternal blood in one thousand cases that an interchange of antigens and antibodies probably does occur between mother and foetus through the placenta but that pathologic effects from this transfer are prevented by some 'protective mechanism'. In 1936 JONSSON showed that A or B agglutinogens present in the foetus of a mother not possessing these agglutinogens could stimulate a rise in titer of the mother's α- or β-agglutinins. This favoured the belief that the pathological conditions in the newborn might be traceable to an A B O iso-immunization. LANDSTEINER'S and WIENER'S discovery of the Rh factor in 1940 overshadowed the significance of A B O immunization, which from then on was given less attention. The question of A B O immunization has, however, again begun to attract interest, especially since it has been found that the Rh factor alone is unable to explain all cases of morbus haemolyticus neonatorum. It is known that other antigens also are capable of producing iso-immunization in a manner similar to that of the Rh factor. Yet it is a fact that an A B O incompatibility between mother and child is common, while morbid conditions in the newborn infants born after such a heterospecific pregnancy are rare. This is probably attributable

to the fact that as a rule A and B antigens are present not only in the tissue cells and the red blood cells but also in various extracellular fluids, and secondly, that the A and B antigens in solution are capable of binding their specific anti-A and anti-B agglutinins, and in this manner forming the above-mentioned 'protective mechanism'. It follows from this that foetal injury due to A and B iso-immunization should be almost entirely limited to non-secretors, i.e. those children in whom the A and B factors, like the Rh factor, are present almost exclusively in the tissue cells and not to any significant extent in the extracellular fluids of the body. It is undoubtedly difficult to produce clear-cut evidence to show that the foetus really can be injured by an immunization in the A B O system, and before drawing conclusions in this respect other causal factors, especially an Rh immunization, must first be excluded. It must also be borne in mind that mothers with substantially elevated anti-A or anti-B titers are able to give birth to completely normal children in spite of the fact that the antibody response is caused by a blood group incompatibility between mother and child (JONSSON, SMITH, AND OTHERS).

Many workers, however, have described cases of a haemolytic disease which they believe to be caused by a placental transfer of A or B antibodies (AUBERT AND ASSOCIATES, POLAYES, DE BURGH AND ASSOCIATES, FORMAGGIO AND OTHERS), while others assume a very sceptical attitude (POTTER AND OTHERS).

Last year some cases were admitted to the Paed. Clinic, Lund, and Flensburg Children's Hospital, Malmö, which are of interest in this respect, inasmuch as one might wonder whether the causal factor was not after all to be sought in an A B O iso-immunization.

Case 1 (671/48 Malmö). Boy, b. July 31, 1948. First child. Normal delivery. Birth wt. 3 230 g. Father: blood group A_1 Rh—N; mother: blood group O Rh + MN. Child: blood group A Rh +. Anti-A agglutinins in mother's blood immediately after partus had a titer of 1 : 3 200 (in twelve sera from O-individuals examined by same method this titer was between 1 : 40 and 1 : 320). No anti-Rh agglutinins detectable in mother's blood. Her blood did not agglutinate blood cells of type CDe/CDe or cde/cde in serum or in a saline solution. Neither did it agglutinate the husband's blood cells after neutralization of the anti-A agglutinins with

purified A-substance. At birth, child showed no symptoms suggestive of icterus but after a few days he began to be indifferent and to show evidence of increasing icterus. On admittance to Flensburg Children's Hospital on Aug. 4, 1948, he was in a bad condition and lay apathetic and relaxed. The skin and the sclerae were very yellow. The spleen was felt just below the arcus but the liver could not be palpated. There were frequent stools with distinct traces of haemorrhage until Aug. 8, after which the child took a turn for the better. He improved, sucked willingly, which was not the case before, and his jaundice began to fade. Other blood examination tests: Aug. 4 haemoglobin (SICCA) 130 %; red blood cells 5.7 million; white blood cells 9 200. Differential count: rod-shaped cells 15; segmented 35; basophiles 1; lymphocytes 15; monocytes 17; erythroblasts 10; other immature cells 7 %. Thrombocytes 232 000. Bilirubin in serum (micromeulengracht) 1 : 100. Prothrombin 50 %. On Aug. 6 haemoglobin 120 %; red cells 5.5 million. Prothrombin 77 %. Aug. 8 haemoglobin 125 %; red cells 5.1 million. Prothrombin 113 %. Therapy: on Aug. 4 and 5 20 ml Rh—O blood intraperitoneally.

Cases 2 and 3 (780/47 Lund). Twins, fourth and fifth children, born Aug. 15, 1947. Parents healthy. Father belonged to blood group A Rh +; mother, to group O Rh +; both twins, to group A Rh +. At partus mother's blood contained agglutinins against A in a titer of 1 : 800 and against B in a titer of 1 : 20. No Rh antibodies could be shown in the mother's blood. Other children: no. 1, girl, b. 1939; no. 2, boy, b. 1941. Both healthy. No. 3: full term, well-developed girl, stillborn 1944. The child died one day before partus. Autopsy was unable to explain cause of death.

Twin I. Girl delivery, occiput. Birth wt. 3 050 g. At birth general condition rather good. On Aug. 18 pat. began to be indifferent and sleepy and stools showed evidence of slight haemorrhage. Internal organs otherwise apparently normal. Treated with blood and K-vitamin intramuscularly. Following day stools still showed traces of blood. Aug. 20 stool thin but free from blood. Aug. 21 an infection of the upper respiratory tract intervened. Commencing occlusion of nostrils and laboured respiration. These troubles increased the following day. Suppressed breathing. Patient treated with penicillin 3 000 × 8 and with blood intramuscularly. On Aug. 25 definite improvement. Blood counts: Aug. 18 haemoglobin (Sahli) 148 %; red cells 4.6 mill.; white 10 600. Differential count: neutrophils 40.5; eosinophils 16.5; basophils 0.5; lymphocytes 32.5; monocytes 10 %. Nucleated red blood cells 3.5 per 100 white blood cells. Prothrombin minimum on Aug. 23 66 %. Lowest count of haemoglobin 90 % and for red cells 2.7 mill., likewise on Aug. 23.

Twin II. Boy delivery, after-coming head. Birth wt. 2 730 g. Relatively good general condition at birth. On Aug. 17 pat. became very

indifferent and his general condition deteriorated substantially. He looked pale and seemed to be in poor condition. No breathing through nostrils, no dyspnoea. During night vomited with traces of blood; stool also contained slight quantity of blood. Towards morning rapidly became worse and died. Therapy: analeptics, K-vitamin, blood injections. Autopsy: cause of death anatomically obscure. Microscopic examination of lungs, liver, spleen, kidneys, and brain stem showed evidence of general hyperaemia, but no traces of haemorrhage were discernible. No anatomical changes suggestive of erythroblastosis.

Discussion

Both mothers belonged to Group O Rh + and all three children to Group A Rh +. The anti-A titer was excessively high in both mothers and they possessed no Rh antibodies. All three children reacted in a conspicuously similar manner. Their symptoms occurred relatively late compared with the haemolytic disease picture which generally appears in an Rh-immunization, and were also of milder type, which has been pointed out as typical of haemolytic diseases due to A B O incompatibility (HALBRECHT, DE BURGH AND ASSOCIATES, and others). Striking, however, was the patients' poor general condition and conspicuous indifference and weakness. These do not accord well with the other mild symptoms. Intestinal bleeding, likewise a symptom more likely to be a subsidiary reaction than the causal factor of the bad condition, was also characteristic of all three. One of the twins died immediately after falling ill. Autopsy revealed no clear-cut cause. That an earlier child of the mother died is also worthy of note. Autopsy was unable to explain the earlier death also. As mentioned above, the symptoms of this disease generally appear late and increase.

This late appearance of the symptoms and their progressive increase has led DE BURGH and associates to consider the possible presence of agglutinins in the breast milk as being responsible for the condition. They write: »It is possible that the agglutinin may have been concentrated to an abnormal degree in the milk or that it is not readily destroyed in the gastro-intestinal tract of the infant.» All three sucked at the mother's breast during the first three days.

The cases described above coincide more or less with some of the cases published earlier. Whether or not the disease is caused by an anti-A reaction is, of course, impossible to decide. But it seems as if the reaction might be responsible.

Summary

A description is given of some cases of haemolytic diseases of the newborn which may have been caused by an A B O incompatibility.

Résumé

Iso-immunisation dans le système A B O et Morbus Haemolyticus Neonatorum

On décrit quelques cas d'affections hémolitiques chez le nouveau-né causées croit on par une incompatibilité A B O.

Zusammenfassung

Iso-Immunisierung im A B O System und Morbus Haemolyticus bei Neugeborenen

Eine Beschreibung von einigen Fällen von hämolytischen Krankheiten bei Neugeborenen wird gegeben. Eine A B O Unverträglichkeit wird hierbei als Ursache der Krankheit angegeben.

Sumario

Iso-Inmunización en el sistema A B O y enfermedad hemolitica del recién nacido

Se describen algunos casos de infermedad hemolitica en el recién nacido, donde se piensa que la causa de la enfermedad es una incompatibilidad con el sistema A B O.

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FROM THE STATE CHEMICO-LEGAL LABORATORY, RH-DEPARTMENT, STOCKHOLM.

The Significance of the Rh Genotype in Erythroblastosis Foetalis

by

BIRGER BROMAN, M.D.

Hitherto it has probably only seldom been possible to assess in man certain genes in both parents by means of laboratory investigations alone and thus to draw conclusions with a high degree of certainty regarding the risks of the occurrence of disease in their children.

Blood-group research has nevertheless afforded us this possibility in respect of the blood group system Rh and familial neonatal erythroblastosis. This disease, which has a very high mortality rate, has many different manifestations and names, such as »icterus gravis neonatorum», »hydrops foetalis» and »haemolytic disease of the newborn».

It has now been demonstrated that the course of this formerly mysterious disease with a familial occurrence is characterized by a pathologically raised haemolysis of the child's red blood corpuscles owing to an isoimmunization of the pregnant woman to a blood group antigen in her own foetus. In such cases, the newly-discovered Rh system plays the main rôle, since an Rh immunization is the determining factor in the genesis of the disease in more than 90 % of the erythroblastotic cases.

During recent years the Rh factor has been shown to consist of an antigen mosaic. The antibodies occurring on the Rh immunization of a woman can be directed against a single Rh partial antigen. In order for a child to develop erythroblastosis, the mother must obviously not only be Rh immunized sufficiently strongly and sufficiently early in pregnancy, but her Rh an-

tibodies must also be directed against one of the Rh partial antigens present in the blood corpuscles of her child.

With regard to the forementioned facts, it can readily be understood that whether a child of an Rh immunized woman will be healthy or not depends on the type of its mother's Rh antibodies and on which Rh gene it has inherited from the father. The Rh genotype of the father is thus of decisive importance.

The Rh chromosome according to Fisher-Race.

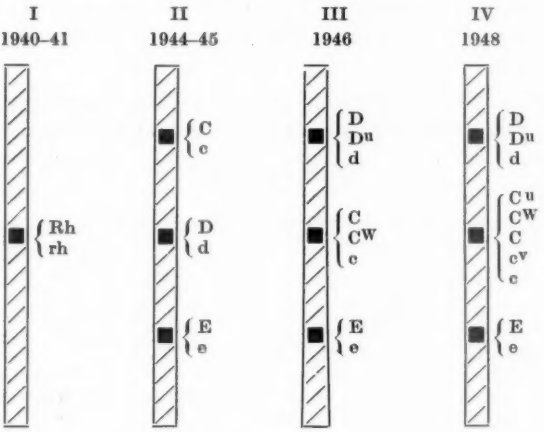


Diagram 1.

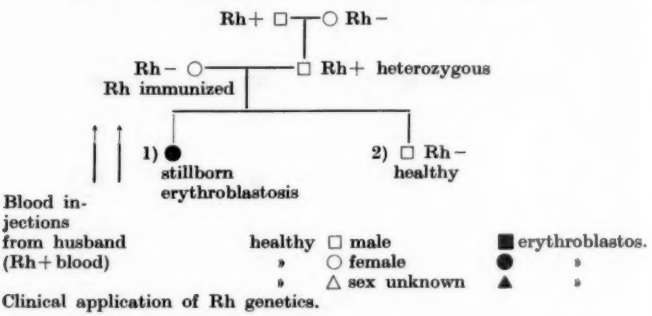
Under such circumstances, the possibility of making a clinical prognosis for an expected child is therefore mainly dependent on the development of the genetics of the Rh system through research in blood-grouping. This science is fortunately undergoing rapid development. Its progress can be divided into four stages (v. Diagram 1). The genetic theory and nomenclature of Fisher-Race will be used in the following.

One condition for the occurrence of an Rh immunization of a woman on the grounds of pregnancy is the presence in her foetus of an Rh antigen lacking in the mother. The most common and best-known kind of Rh immunization — and earlier the only

established kind — is that of an Rh negative woman in whom antibodies occur that act on Rh positive red blood corpuscles. If the husband of such a woman is homozygous Rh positive, it follows that all the children will be Rh positive and erythroblastotic. If, however, the father is heterozygous Rh positive, a baby has a 50 % chance of being Rh negative and healthy.

In the first stage of the Rh epoch, elucidation of the father's genotype was possible only by means of familial investigations. The father's parents and his children were studied. If one of them was Rh negative, the father himself had an Rh negative gene and was heterozygous. Such an example is demonstrated in Diagram 2.

Case of an Rh immunized mother with a *heterozygous* Rh positive husband and an Rh negative healthy child.



Clinical application of Rh genetics.

Diagram 2.

On the other hand, it was more difficult to diagnose an individual as a homozygous Rh positive. This could be presumed only if there were many children all of whom were Rh positive. An example is shown in Diagram 3.

During the second stage, the discovery of the Rh sub-groups by means of the use of the different varieties of Rh antibodies in Rh testing complicated the situation. At the same time, however, it allowed the genotype of an individual to be judged with a great degree of probability by testing a sample of his blood only, without making a familial investigation.

Case of an Rh immunized mother with a *homozygous* Rh positive husband.

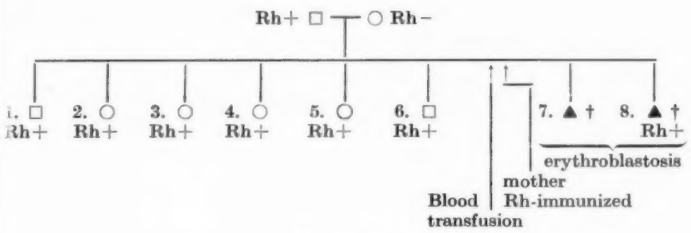


Diagram 3.

Only the four most common Rh anti-sera, *i.e.* anti-C, anti-D, anti-E and anti-c, are generally available in ordinary laboratories. There may even be difficulties at times in obtaining these sera. With these four anti-sera it is possible to some extent to make accurate prognoses with regard to the children of an Rh immunized woman. As an example can be cited the forementioned family with a large number of children. The results of the typing are seen in Diagram 4. After typing the husband with the four anti-sera, his genotype was assumed to be CDe/CDe. In actual fact, this assumption was in agreement with the results of the typing of the children.

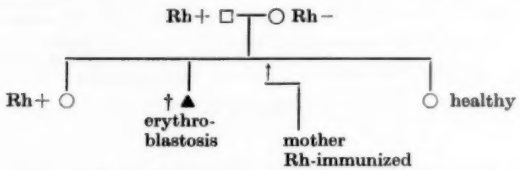
Typing.

	Anti- C	D	E	c	Most Probable Rh Genotype
Father	+	+	—	—	C D e / C D e
Mother	—	—	—	+	c d e / c d e
Child 1.	+	+	—	+	C D e / c d e
2.	+	+	—	+	C D e / c d e
3.	+	+	—	+	C D e / c d e
4.	+	+	—	+	C D e / c d e
5.	+	+	—	+	C D e / c d e
6.	+	+	—	+	C D e / c d e
8.	+	+	—	+	C D e / c d e

Diagram 4.

At times, however, such an investigation can be misleading and the genotype of the husband proves to be another than that assumed. Under such circumstances, a child may unexpectedly be healthy (v. Diagram 5).

Case of a healthy child of an Rh negative and Rh immunized woman with a "homozygous" Rh positive husband.



	C	D	E	c	Most Probable Genotype
Father	+	+	+	+	C D e/c D E
Mother	—	—	—	+	c d e/c d e
Child 3	+	—	—	+	C d e/c d e

The father's true genotype is C d e/c D E.
The mother's serum contains only anti-D.

Diagram 5.

In other instances, investigations with these four sera fail to solve the problem and it is only with the aid of the knowledge gained during the third stage of the Rh epoch that it can be elucidated.

Diagram 6 shows a family with four healthy children followed by three suffering from erythroblastosis. Both the parents and all the children tested were Rh positive. The last of the affected

Case of familial erythroblastosis with Rh positive parents but nevertheless due to Rh immunization.

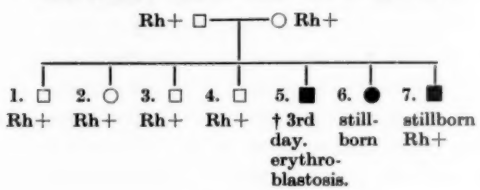


Diagram 6.

children was tested with the four Rh anti-sera. It was not, however, possible with their aid to prove that the child possessed an Rh antigen lacking in its mother.

The use of another anti-serum, anti-C^w, discovered during the third stage of the Rh epoch, makes it possible to demonstrate the antigenic differences between mother and child (v. Diagram 7). In the foremention case, the mother's serum actually contained the anti-C^w antibody.[1]

	I	II					III		
	Anti Rh	Anti- C	D	E	c	Most Probable Genotype	Anti- C+C^W	C^W	Most Probable Genotype
Father	+	+	+	+	+	C D e/c D E	+	+	C^WD e/c D E
Mother	+	+	+	—	+	C D e/c d e	+	—	C De/c d e
Child 1.	+	+	+	+	+	C D e/c D E	+	—	C De/c D E
2.	+	—	+	+	+	c D E/c d e	—	—	c DE/c d e
3.	+	+	+	—	—	C D e/C D e	+	+	C^WD e/C D e
4.	+	+	+	—	+	C D e/c d e	+	+	C^WD e/c d e
7.	+	+	+	—	+	C D e/c d e	+	+	C^WD e/c d e

The mother's serum contains anti C^W.

Diagram 7. No antigenic difference could be demonstrated between the mother and the affected child (No. 7) on investigation with the known anti-sera of the epochs I and II. In the third epoch, however, it was possible to show that the child possessed a C^W antigen lacking in the mother.

In another instance, a healthy Rh positive baby was quite unexpectedly born to a previously Rh immunized Rh negative woman (v. Diagram 8). Testing with the usual four Rh typing sera failed to explain the child's freedom from disease. This problem was, however, solved later, since in the third stage of the Rh era it was found that in the D-d position there were further allelomorphs, collectively known as D^u. This discovery made it possible to show that, in the foregoing case, there was a difference in the D factor of the donor and the D factor of the husband and

[1] The writer is indebted to Dr. R. R. Race and Dr. S. Lawler of the British Medical Research Council's Blood Group Research Unit, London, for confirmation of the type of antibody found in this case.

Case of healthy Rh positive child of a previously Rh immunized mother.

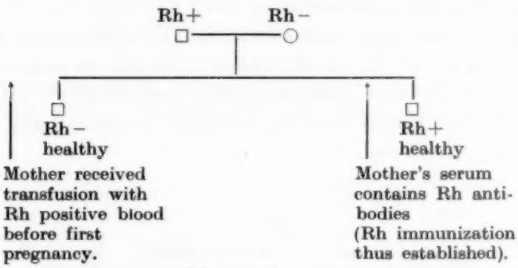


Diagram 8.

child, the two last-mentioned being of the D^u type. The donor's blood presumably immunized the mother, and her serum contained an antibody of the pure anti-D type that did not act on the red blood corpuscles of the husband and child (v. Diagram 9). Using the red cells of the husband and child as test cells, even the indirect Coombs' reaction was negative with the serum of this mother.

Typing.

	II					III		
	Anti- C	D	E	e	Most Probable Rh Genotype	Anti- D+D^u	Pure D	Most Probable Rh Genotype
Father	+	+	—	+	C D e/c d e	+	—	C D^u e/c d e
Mother	—	—	—	+	c d e/c d e	—	—	
Donor	+	+	+	+	C D e/c D E	+	+	C D e/c D E
Child 1.	—	—	—	+	c d e/c d e	—	—	
2.	+	+	—	+	C D e/c d e	+	—	C D^u e/c d e

The mother's serum contains a pure D of the blocking or "incomplete" type.

Diagram 9.

The clinical significance of the evolution of the genetics of Rh in the fourth stage is not yet established, but can easily be envisaged.

In the beginning of the 1940's, many authors doubted the correctness of Levine's theory regarding the pathogenesis of erythroblastosis foetalis on the basis of Rh immunization, since it was impossible in many cases of the disease to demonstrate the Rh agglutinin in the serum of the mother. It was nevertheless soon found that with the use of a special technique, a formerly unknown type of Rh antibodies — i.e. the so-called blocking or incomplete antibodies — could instead be demonstrated in these cases. These mothers with no Rh agglutinin were thus only apparent exceptions to the theory of isoimmunization.

It has now occasionally been found instead that a previously Rh immunized woman can give birth to healthy Rh positive children. The truth of Levine's theory in many cases of erythroblastosis is therefore once more questioned. Thus, Bruce Chown stated that in a series of 48 Rh positive viable offspring of earlier Rh immunized women, he found no less than 13 healthy children. Chown pointed out »... that other factors than blood incompatibility play an important, at times a deciding, role in the development or non-development of erythroblastosis».

The present writer's experiences described in the foregoing give, on the contrary, further proof of the overwhelming rôle that must usually be accorded to incompatibility of blood for the development of *familial* erythroblastosis foetalis. Exceptions to this rule are often found, on more thorough serological analysis, to be apparent only. Instead of contradicting the central importance of isoimmunization in the occurrence of the familial erythroblastotic disease, such »deviations» thus strengthen its position.

In the opinion of the writer, these cases also demonstrate the necessity of highly-qualified blood group laboratories for clinical work. In smaller countries, such as Sweden, *one* central laboratory that can have access to most of the essential types of sera is required.

If a local pathologist or serologist, with access only to a few different kinds of typing sera, makes blood investigations in cases such as those mentioned here, there is considerable risk that an erroneous interpretation of the conditions will result.

Summary

The author gives an account of recent advances in the serology of the Rh blood groups and of some typical cases of erythroblastosis foetalis. Many »deviations» from Levine's theory concerning the origin of erythroblastosis have proved to be only apparent, as is shown by the cases related.

Résumé

L'auteur a cité les progrès récents de la sérologie des groupes sanguins Rh et quelques cas typiques d'érythroblastosis foetalis. De nombreuses »déviations» de la théorie de Levine sur l'origine de l'érythroblastosis ne se sont révélées qu'apparentes, comme on l'a vu par les cas relatés.

Zusammenfassung

Der Verfasser berichtet über neue Fortschritte in der Rh Blutgruppen-Serologie und über einige typische Fälle von Erythroblastosis foetalis. Viele Abweichungen von der Levineschen Theorie über den Ursprung der Erythroblastosis haben sich als nur scheinbar erwiesen, wie aus den berichteten Fällen hervorgeht.

Sumario

El autor cita varios progresos recientes en la serología de los grupos de sangre Rh y evaluado casos de fetalis eritroblastósis. Muchas de las desviaciones de la teoría de Levine respecto al origen de la eritroblastósis se ha probado que son sólo aparentes, como se desprende de los casos descritos.

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Parenteral Fluid Therapy in Diabetic Coma

by

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Repair of the losses sustained in the starvation and dehydration incident to diabetic coma is an essential part of the therapy of this serious metabolic disorder. Indeed, though provision of adequate insulin is a primary therapeutic consideration, insulin without such repair therapy as will permit reestablishment of normal cellular anatomy and function may be of limited effectiveness.

A careful history which reveals the precipitating cause of the coma and the duration and severity of the metabolic disturbances should permit a qualitative estimate of the depletion, acidosis, and dehydration and the extent of the therapeutic problems and difficulties that may be encountered. But physiologic parenteral repair therapy during the period when the patient is in a critical state and is unable to ingest nutrients orally because of nausea demands quantitative appraisal of both intra- and extracellular losses and metabolic needs. Though blood haemoglobin or serum protein concentration may reflect haemoconcentration, a single determination may not be a reliable index of the degree of dehydration (1). Moreover, concentration measurements of urine obtained at the time the patient is first seen and of blood and plasma constituents without appropriate determination of volume cannot be used to estimate losses sustained and therapeutic replacement needs (1). Therefore, a quantitative understanding of the metabolic losses sustained by and maintenance needs of the average diabetic coma patient is essential to optimal therapy (2—6).

The purpose of this paper is to present data pertinent to such an understanding of the parenteral fluids needs.

Table I presents theoretical calculations of losses incident to a dehydration resulting in a 10 % reduction in body weight and affecting equally extra- and intracellular fluid volumes, as suggested by available evidence (2, 3, 7—12). They also assume no change in body fluid concentrations.

Table I

Approximate body fluid composition per kg of body weight and calculated losses incident to a dehydration resulting in a 10 % decrease in the body weight, assuming an equal loss from extra- and intercellular fluids and maintenance of normal body fluid concentrations.

T = total; E = extracellular; and I = intracellular.

	$(H_2O)_T$ ml	$(H_2O)_E$ ml	$(H_2O)_I$ cc	Na_E mEq.	Cl_E mEq.	Na_I mEq.	K_I mEq.
Composition per kg..	720	220	500	31	25	4	70
Dehydration Losses per kg	100	50	50	7	6	0.4	7

It should be noted that such a 10 % loss of body weight due largely to dehydration means a 14 % loss of total body water, a 23 % loss of extracellular water and electrolytes, and a 10 % loss of intracellular water and electrolytes. These losses are overall losses including renal and extrarenal losses.

Table II presents the actual losses sustained by an individual during 4 days of complete thirsting and starvation. Because the losses, particularly of Na and Cl, for the first 2 days of starvation and thirsting reflect variations dependent upon the uncontrolled foreperiod metabolic state, the data of the fourth day are given separately as basic daily losses due to thirsting and starvation.

The urinary losses given in Table II do not include the insensible losses of such electrolytes as Na and Cl. Roughly estimated values are, therefore, added. The loss of 3 mEq of K as compared to 7 in Table I reflects the concentration of cell K which occurs during the dehydration of thirsting. There is, how-

Table II

Losses suffered during 4 days of complete thirsting and starvation by R.E., a normal adult weighing 64 kg.

Days	Losses					
	Weight kg	Na mEq.	Cl mEq.	K mEq.	P g	N g
1—3	4.40	247	209	130	2.6	31
4	1.45	45	33	59	1.2	13
Total	5.85	292	242	189	3.8	44
per kg	0.09	4.6	3.8	3	0.06	0.7
Insensible[1] per kg		1.5 ±	1.5 ±			

[1] Assuming a loss from perspiration of 700 ml per day with Na and Cl concentrations of approximately 25 % of extracellular fluid concentrations.

ever, an excessive loss of K from cells relative to N, as the ratio of mEq. K lost to g N lost is 4.3 compared to the ratio of 2.8 of muscle tissue. This excessive loss of K above N from tissue appears characteristic of starvation and dehydration (2—15). It means, of course, that rehydration of the dehydrated tissue will result in low intracellular K concentration unless K is made available in the rehydration therapy.

Table III presents the losses incurred by a diabetic patient during the development of pre-coma acidosis incident to withdrawal of insulin for 3.4 days plus extrapolated losses of an added theoretical day of no water or fluid intake due to nausea and vomiting. Further details of this metabolic study have been reported (3). Such extrapolation for another day was necessary as insulin and hydration therapy were administered in consideration of the patient before he suffered such nausea and dehydration as are commonly encountered in diabetic coma. The losses of this added day are compounded from the losses sustained the fourth day of thirsting, Table II, plus those calculated due to the caloric and water losses incident to the glycosuria of this diabetic and to 500 ml of vomitus. Both the actual losses of the 3.4 days and the total losses give a K/N ratio of approximately 7, thus showing a specific loss of K from tissue in excess of N even

greater than in non-diabetic starvation and dehydration. If the diabetic, as available data suggest (3), cannot concentrate urine to the normal high value of 1.4 milliosmoles per ml (16), then the weight or water loss of the added extrapolated day may be too small.

Table III

Losses suffered by 68 kg diabetic during withdrawl of insulin for 3.4 days with occurrence of pre-coma acidosis and nausea plus extrapolation of losses for added theoretical day of vomiting and thirsting. (3).

Days	Losses						
	Weight kg	Na mEq.	Cl mEq.	K mEq.	Mg mEq.	P g	N g
3.4	3.7	217	142	273	41	3	40
1.0 (added)	2.9	105	130	115	12	2	20
Total	6.6	322	272	388	53	5	60
per kg	0.1	5	4	6	0.8	0.07	0.9
Insensible per kg		1.5 ±	1.5 ±				
Conc. per l.		65	55	30[1]	4.0[2]	0.2[2]	

[1] Assuming only half loss is immediately replaceable by parenteral therapy.

[2] Assuming one quarter is replaceable.

However, for our orienting purposes the data of the 3 tables suffice. For weight or water, Na and Cl, the agreement is somewhat reassuring. The order of magnitude of the absolute K loss in the diabetic and the ratio of K loss to N would appear to represent the proper order of magnitude.

Parenteral Therapy Implications

In applying such estimation of losses to replacement therapy consideration should be given the fact that the losses reparable in the first 24 hours of therapy do not include those referable to tissue oxidation. Such losses can be repaired only by the deposition of new tissue and fall outside the scope of rehydration

therapy. Thus for example rehydration therapy concerns that portion of the K loss that is in excess of the N loss; i.e. approximately 3 mEq. K per kg rather than the 6 mEq. given in Table III. Moreover, since body water is proportional to body tissue, the rehydration required in the first 24 hours will be accomplished by less than 100 % replacement of water loss. The repair requirements for the first 24 hours of therapy in terms of per cent of losses incurred may, therefore, be estimated as H_2O, Na, and Cl 80 %, K and Mg 50 %, P 25 %, and N 0 %.

From such considerations the replacement needs of the first 24 hours of therapy approximate per kg: H_2O, 80 ml; Na, 6 mEq.; Cl, 5 mEq.; K, 3 mEq.; Mg, 0.4 mEq.; and P, 0.02 g. Because these losses represent a per cent of body mass, they are expressed on a per kg basis. During this 24 hours the patient's maintenance requirements (17) must be provided in addition to the repair needs. The maintenance requirements, however, are prescribed by physiologic functions which are proportional to square meters of body surface, not to kg of body weight. Table IV presents the basic maintenance requirements of

Table IV

Basic parenteral maintenance requirements per sq.m. body surface of a diabetic during first 24 hours of therapy.

Requirement	H_2O ml	Na mEq.	Cl mEq.	K mEq.	Mg mEq.	P g	Glucose g
Insensible[1]	500	11	11	2			
Renal —							
normal basic[2]	250	6	6	10	3	0.2	
added diabetic[3]	750	12	11	10	4	0.4	50
Caloric							250
Total	1 500	29	28	22	7	0.6	300
Concentration per l...	1 000	20	19	13	5	0.4	200

[1] Assuming perspiration accounts for 70 % of insensible loss and has Na and Cl concentrations of 25 % of the extracellular fluid concentration.

[2] Determined by experimental data on normal subjects.

[3] Determined by metabolic balance data on diabetic coma patients during therapy.

a diabetic per sq.m. of body surface during the first 24 hours of parenteral fluid therapy.

From the data of Tables III and IV the total repair and maintenance requirements per sq.m. of body surface of the first 24 hours of treatment may be estimated. Table V gives such total therapeutic needs. To correct such data for a patient of any specific size multiply the repair data of the table by weight in kg divided by 30[1] and the maintenance data by sq.m. of body surface. For the adult of 70 kg or 1.7 sq.m. the approximate concentrations of Na, Cl, and glucose in the parenteral fluid are 60 mEq., 50 mEq., and 55 g per liter respectively. For the child of 10 kg or 0.5 sq.m. corresponding figures are found to be 50, 40, and 100.

Table V

Repair and maintenance parenteral therapy of first 24 hours of treatment for a child of approximately 30 kg or 1 sq.m. body surface.

	H_2O ml	Na mEq.	Cl mEq.	K mEq.	Mg mEq	P g	Glucose g
Repair (per kg × 30)	2 400	180	150	90	12	0.6	0
Maintenance (per sq. m × l)	1 500	31	30	22	7	0.6	300
Total	3 900	211	180	112	19	1.2	300
Aprox. Conc. per l ..	1 000	55	45	30	5	0.3	75

The data make it clear that physiologic saline (i.e. 150 mEq. Na and Cl per liter) is excessively hypertonic in Na and Cl in terms of the physiologic needs. If the water requirement were met by providing such a solution (18), 5 times the required amount of Cl would be provided. If sodium bicarbonate or sodium lactate is used, as frequently recommended to correct the serum CO_2, the total sodium administered in the first 12 hours of therapy may be as much as 20 mEq. per kg or 3 times the 24 hour need (19). As seen by the data and as pointed out several times (20, 21),

[1] For an individual of average body configuration 1 sq.m. body surface = 28 kg.

provision of appropriate amounts of Na and Cl with a ratio of Na/Cl of extracellular fluid or 1.3 satisfies the Na and bicarbonate need. Increasing evidence (5, 6, 22—28) indicates that provision of larger amounts of Na without K to the individual whose cells are depleted of K results in a syndrome of peripheral muscle paralysis, respiratory muscle weakness with shallow gasping respiration, and myocardial failure with weak, rapid pulse and ashen grey pallor. This syndrome may lead to fatal cardiac and respiratory failure 8 to 28 hours after beginning therapy in spite of earlier improvement in clinical signs and correction of the serum Na, Cl, CO_2, and glucose concentrations to normal values (3—6, 26—28).

The Actual Administation of Parenteral Fluids

Such a solution as indicated in Table V, though appropriate for the total needs over the first 24 hours, cannot be used as initial parenteral fluid therapy. Too often the patient's circulation and renal function is impaired. The serum K may be elevated to double and the inorganic P to triple the normal values (5, 29, 30). Under such circumstances administration of a solution containing 30 mEq. K and 300 mg P per liter may result in serious toxic effects. Until further experience is available, therefore, it appears desirable to begin therapy with some such solution as 65 millimols of NaCl and 25 millimols of $NaHCO_3$ or Na lactate per liter. Approximately 500 ml per sq.m. of body surface should be administered at approximately 8 ml (140 drops) per minute. Following this a transfusion of 300 ml per sq.m. should be considered, particularly in terms of the patient's deficits in haemoglobin and serum protein. Then, if the patient is voiding and the circulation is satisfactory, an appropriate hypotonic multiple electrolyte solution may be started. During the past several years our Children's Medical Service at the Massachusetts General Hospital has been using a solution[1] more hypotonic than suggested by the concentrations in the last line of Table V.

[1] A solution containing the following mEq. per liter: Na 30, Cl 22, K 20 and lactate 20: the glucose being from 2—10 g per 100 cc as needed to satisfy the caloric needs.

Using such a solution for parenteral fluid therapy based on repair and maintenance needs as outlined above and administered with precautions to avoid toxicity from K (5, 30) we have during the past several years obtained excellent clinical results without evidence of toxicity in the rehydration of several hundred patients suffering dehydration with acidosis from diabetes (4—6), diarrhoea (31, 32), or burns, and also with alkalosis from vomiting or postoperative dehydration and alarm reaction (33).

Particularly in the treatment of diabetic coma more P than provided in this solution seems indicated as serum inorganic P levels of less than 1 mg per 100 cc. have been observed during the course of our therapy (6). Much larger amounts have been administered by us and others (29) without abnormal elevation of serum phosphorus. In view of the role of Mg in the utilization of glucose, the tissue need of Mg, as indicated by balance studies (3) and serum concentrations as low as 0.5 mEq. per liter during therapy (6), and the lack of toxic symptoms until serum Mg exceeds 6 mEq. per liter (34), the provision of 5 mEq. Mg per liter in the parenteral therapy appears appropriate.

We, therefore, are now changing our basic parenteral rehydration solution to one containing the following concentrations per liter:[1] Na 53 mEq., Cl 45 mEq., K 25 mEq., Mg 5 mEq. and P 0.2 g. The K and P concentrations are reduced below the concentrations given in Table V to avoid the possibility of exceeding the renal excretory capacity if more than the specified amount of infusion should be given.

The rate of administration of the multiple electrolyte solution should approximate 3 ml (50 drops) per sq.m. of body surface per minute. The duration of parenteral therapy varies according to the persistence of nausea. Usually 70 % of the 24 hour requirement given parenterally in 12 hours will result in such improvement that the remainder may be given orally. When the fluid can be given orally, it may be flavored with ginger ale, orange juice, or diluted with milk.

[1] Made by adding 2.8 g Na lactate, 1,8 g NaCl, 1.0 g KCl, 1.0 g K_2HPO_4, 0.3 g $MgCl_2$ and 0.15 g $NaH_2PO_4 \cdot H_2O$ (PH 7.4) to 1 liter of 5—10 % glucose. The $MgCl_2$ is autclaved and added separately as it causes cloudiness if autclaved with PO_4.

Summary

The extra- and intracellular losses incident to diabetic coma are presented.

Maintenance requirements during the first 24 hours of therapy are estimated.

The repair and maintenance needs thus defined by metabolic balance data and clinical experience indicate the unphysiologic nature of so-called physiologic saline in the parenteral fluid therapy of diabetic coma.

The total parenteral fluid therapy to repair the losses and meet the maintenance requirements during rehydration is indicated.

The manner of providing the parenteral rehydration is described.

Résumé

Description des pertes extra- et intracellulaires accompagnant le coma diabétique.

Les besoins vitaux pendant les premières 24 heures de la thérapeutique sont estimés. Les besoins vitaux et réparateurs ainsi définis par les données de la balance métabolique et l'expérience clinique révèlent la nature non-physiologique de la saline dite physiologique dans la thérapeutique fluide parentérale du coma diabétique.

La thérapeutique fluide parentérale totale pour réparer les pertes et pour satisfaire aux besoins vitaux pendant la réhydratation sont indiqués.

Et la manière d'assurer la réhydratation parentérale est décrite.

Zusammenfassung

Die extra- und intra-zellulären Verluste, die beim diabetischen Koma vorkommen, werden dargestellt.

Der Erhaltungsbedarf während der ersten 24 Stunden der Behandlung wird untersucht.

Der Wiederherstellungs- und Erhaltungsbedarf, genau definiert durch Angaben über das Stoffwechsel-Gleichgewicht wie

durch klinische Beobachtung, zeigt die unphysiologische Natur der sog. physiologischen Salz-Lösung bei der parenteralen Flüssigkeits-Therapie des diabetischen Komas.

Die gesamte parenterale Flüssigkeits-Therapie zum Ausgleich der Verluste und zur Sicherung des Erhaltungsbedarfes während der Rehydration wird angegeben.

Die Methode der parenteralen Rehydration wird beschrieben.

Sumario

Se informa sobre las pérdidas extra e intercelulares ocasionadas por coma diabética.

Se estiman las necesidades de mantenimiento durante las primeras 24 horas de terapia.

Las necesidades de reparo y mantenimiento, así definidas mediante datos de equilibrio metabólico y experiencia clínica, indican la característica no fisiológica de la llamada sal fisiológica en la terapia del flúido parentérico de la coma diabética.

Se indica la terapia del flúido completamente parentético para reparar las pérdidas y para cumplir con las necesidades de mantenimiento durante la rehidratación.

Se describe la manera de proporcionar la rehidratación parentérica.

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FROM THE PAEDIATRIC CLINIC OF KAROLINSKA INSTITUTET AT KRONPRINSESSAN LOVISA'S CHILDREN'S HOSPITAL, STOCKHOLM.
CHIEF: PROF. A. LICHTENSTEIN.

Congenital Hyperplasia of the Adrenals With Adrenal Cortical Insufficiency

by

LARS-ERIK CARLGREN

In 1940 DIJKHUIZEN and BEHR described four cases of adrenal hypertrophy in young infants and mentioned this condition as a new clinical syndrome. All of these cases presented in the neonatal period a very peculiar clinical picture characterized by vomiting, dehydration, and sudden collapse, and all died shortly after the onset of the disease. The only noteworthy finding at autopsy consisted of greatly enlarged adrenal glands which together weighed between 22 and 34 g (normal weight c. 5 g) and displayed a strangely gyrated surface. The microscopic picture was described in detail. The same authors also cited a number of cases from the literature which appeared to be of the same kind; these had been studied principally from the pathologico-anatomical point of view. Since then a number of other authors, among them SKELTON (1945), HARRIS (1946), and ALLIBONE, BAAR, and CANT (1947), have reported similar cases.

DIJKHUIZEN and BEHR were unable to explain the clinical symptoms. Reports from the American literature of cases surviving beyond infancy show, however, that there is adrenal insufficiency with respect to water and electrolyte hormone which can be compensated for by administration of sodium chloride and desoxycorticosterone acetate. In these cases, which have all been of the male sex, macrogenitosomia and precocious skeletal development soon appeared, indicating increased androgenic production by the adrenal cortex.

The case described by BUTLER, ROSS, and TALBOT in 1939 is still alive. According to a personal communication from Dr. TALBOT, the patient gets along well by taking extra salt with his food. Because of precocious skeletal fusion he stopped growing at the height age of nine and now, at the age of eleven, he is much too short. His muscles are extraordinarily well developed and the genitalia very large. The testicles are tumourously enlarged through what appear to be aberrant adrenal cortical cell rests (biopsy). He has a full growth of facial, axillary, and pubic hair. Emotionally he is noisy and somewhat hyperactive. Enormous quantities of 17-ketosteroids are excreted in his urine. He still suffers from disturbances in water and salt metabolism which become manifest whenever the administration of sodium chloride is discontinued.

The case described by THELANDER and CHOLFFIN (1941) required both salt and desoxycorticosterone acetate, and, like the preceding patient, showed markedly precocious skeletal and genital development. According to a later report by THELANDER (1946) the patient died at the age of six in connection with measles. Autopsy revealed, as was anticipated, bilateral hypertrophy of the adrenals (36 and 38 g); the histological picture was very similar to that described by, among others, DIJKHUIZEN and BEHR. Aberrant adrenal cortical rests were found in the testes.

DARROW's case (1944), which resembled the two preceding in all significant details, was treated with sodium chloride and desoxycorticosterone acetate. According to a personal communication from the author, this boy died in another hospital at the age of about five years. The final episode leading to death seemed to have been largely cardiac. At autopsy a large heart and large adrenals were found.

The case described in 1940 by WILKINS, FLEISCHMAN, and HOWARD differs from the others in that there were no symptoms of adrenal cortical insufficiency in infancy. From the age of about one year on, however, the boy craved salt and died at the age of three and a half of adrenal cortical insufficiency. Autopsy revealed bilateral hypertrophy of the adrenal cortex due to an abundance of what was thought to be androgenic tissue. Cell rests resembling those in the adrenals were also found in the testes.

Other cases have been described of pseudohermaphroditism and macrogenitosomia praecox in older children in which diffuse hyperplasia of the adrenals has been found, but no symptoms of cortical insufficiency. These are outside the scope of this article, however.

Congenital adrenal hyperplasia with symptoms of cortical insufficiency in early infancy is clinically a well delimited syndrome which occurs with striking frequency in siblings. Even

though some cases may have escaped diagnosis, the disease is probably unusual, a circumstance which explains to some extent why it is so little known. For example, it is not included in WERGELAND's (1949) survey of the diseases which cause familial deaths in infancy and early childhood. Hence it may be advisable briefly to outline the disease picture before proceeding to presentation of the author's own cases.

The aetiology is unknown. As has already been said, the disease often occurs in siblings; thus a familial factor evidently plays a prominent part in the pathogenesis. It has never been established in more than one generation, on the other hand (WILKINS and others). Boys and girls suffer from it to about the same extent, but while the latter are nearly always pseudohermaphrodites, boys show as a rule no external abnormalities at birth.

The anatomical basis of the disease consists of hyperplasia of the adrenal cortex. Upon microscopic examination the latter proves to consist of tissue rich in cells, unlike that of the normal adrenal cortex. Opinions still differ concerning the type of cell which gives rise to this hypertrophy and the nature of the secretion they produce.

The clinical symptoms are of two kinds. One group is due to reduced or non-existent production of salt- and water-regulating hormone and thus resembles those encountered in Addison's disease. These symptoms include loss of appetite, vomiting, diarrhoea (sometimes obstipation), fatigue, dehydration, cyanosis, and collapse. The vomiting may be very violent and suggest partial obstruction of the digestive tract; in some cases laparotomy has even been performed. Pigmentation of the skin and mucous membranes has also been described. As in Addison's disease, the serum chloride and, especially, the serum sodium are lowered, while the serum potassium and non-protein nitrogen are raised. The urine contains pathological quantities of chlorides. In all the cases examined the blood sugar was normal even when the patient was in a state of collapse.

The other group of symptoms is due to overproduction of the androgenic hormone. In girls this results in pseudohermaphroditism, nearly always present even at birth. In boys the

virilizing effect does not appear until a few months have passed or even later. It takes the form of macrogenitosomia, growth of pubic hair, deepening of the voice, and precocious skeletal development. The increased androgenic activity is also reflected in increased excretion of urinary 17-ketosteroids, with values approaching those of the adult.

Diagnosis is difficult, provided one is not sufficiently familiar with the disease picture to consider the possibility of adrenal insufficiency. In newborn infants hypospadias or similar genital malformations combined with vomiting, loss of weight, and attacks of circulatory collapse should immediately suggest adrenal hyperplasia. In boys diagnosis is considerably more difficult, since they show no outward signs at first of increased androgenic production. When pyloric stenosis or other partial intestinal obstruction can be excluded, adrenal insufficiency should be suspected in connection with the more or less sudden onset of continuous vomiting; loss of weight and dehydration out of proportion to the amount vomited; and a tendency to cyanosis and collapse. Low serum sodium, high serum potassium and nonprotein nitrogen, and excretion of large amounts of chlorides in the urine lend further support to the diagnosis, which may be considered certain if the patient responds promptly to specific treatment with salt and desoxycorticosterone acetate.

Adrenal insufficiency in early infancy may possibly occur without marked anatomical changes in the adrenals. JAUDON (1948) recently described five cases of infantile adrenal insufficiency in which all specific treatment could be discontinued after seven to twenty-nine months. The patients were all boys and showed exactly the same clinical picture as in congenital adrenal hyperplasia except that there was no macrogenitosomia. In only two cases was there a slight increase in the excretion of urinary 17-ketosteroids. The family history was positive in none of the cases, but in three of them the patient was the only child. In early infancy differential diagnosis between this type of transient adrenal insufficiency, the anatomical basis of which is unknown, and adrenal insufficiency due to congenital hyperplasia may be very difficult, since even in the latter there are

at first no exterior indications of increased androgenic production. Under such conditions permanently increased excretion of urinary 17-ketosteroids speaks in favour of hyperplasia, as does a positive family history.

As shown by the survey of the literature, in congenital adrenal hyperplasia with cortical insufficiency the prognosis is extremely grave. Almost all of the cases described hitherto have died in early infancy. In the few who have survived disturbances in the salt and water metabolism have persisted and there has been abnormal sexual development.

Adequate treatment is provided in these cases by administration of sodium chloride and desoxycorticosterone acetate. The former may be given by mouth except when there is violent vomiting and collapse, when it must be administered parenterally. Desoxycorticosterone acetate is given intramuscularly in sesame oil; if one wishes to avoid the daily injections a crystalline suspension may be attempted and is probably preferable to pellet implantation, which is technically difficult to carry out and has too prolonged and therefore uncontrollable an effect. There is no general dosage; ordinarily at least 1.5 à 2 mg per day is necessary. Some cases get along with salt only, however (2 to 5 g and even more per day). As in Addison's disease, if treatment with desoxycorticosterone in combination with salt is too intensive, there is danger of oedema. The possibility of myocardial injuries and damage to the kidneys has also been pointed out.

In these cases operative treatment, which has been attempted in a few cases of adrenal hyperplasia in older children without cortical insufficiency, must be considered too dangerous. Moreover, the chances of being able to correct overproduction of androgenic hormone by unilateral or partial bilateral adrenalectomy are presumably very slight. The androgenic tissue is said to be fairly insusceptible to x-ray therapy (THELANDER 1946).

During recent years three cases with the syndrome described here have been treated at Kronprinsessan Lovisa's Children's Hospital. The first two, who died after a short period of illness, were not diagnosed before death and therefore underwent very incomplete clinical examinations. The third is one of the few

known cases to survive early infancy and will therefore be described in more detail.

Case 1. D. 1050/46. Girl (pseudohermaphrodite), the only child of healthy parents. B. Aug. 29, 1946. Birth wt. 4 050 g. Sex could not be determined at birth. Sept. 25 vomiting began, sometimes projectile. Oct. 3 admitted Medical Dept. Kronprinsessan Lovisa's Children's Hospital under suspicion of pyloric stenosis. Wt. 3 420 g. Considerably dehydrated with haemoconcentration (hgb. 20.6 g, RBC 5.5 mill., haematocrit 65 %, serum protein 7.9 g%); slow, irregular breathing; and tendency to cyanosis and peripheral coolness. No visible ventricular peristalsis. Bowel movements greenish-yellow, rather frequent, somewhat slimy. X-ray examination of abdomen: normal. Treated with blood transfusion, parenteral administration of fluids, and stimulants, but died after six days. Autopsy revealed hypertrophy of the adrenals, which together weighed 18 g. Microscopic examination (K. LINDBERG)[1]: »Upon being stained with Ponceau-fuchsin, an abundance of cells with fuchsinophil cytoplasm, here and there even granulated, though not markedly so, was observed within the cortex. The latter showed for the most part a distinct radial structure, with the cells arranged in columns. A large part of it was evidently made up of foetal cortex with signs of degeneration. The internal genitalia were female.» D.: pseudohermaphroditism + adrenal hyperplasia.

Case 2. A.T. 368/46. Boy. Fourth child of healthy parents. Two siblings, a brother and a sister, well; another brother died at birth of cerebral haemorrhage. B. March 11, 1946. Birth wt. 4 600 g. Unwilling to nurse at breast from beginning: gradually became more and more disinterested. Steady decrease in wt. At age of fourteen days vomiting began, at times projectile. March 27 admitted to Medical Dept. Kronprinsessan Lovisa's Children's Hospital, where nothing abnormal was observed except the aforementioned lethargy and moderate dehydration with haemoconcentration (hgb. 20.2 g, RBC 5.2 mill.). Treated with »fenedrin» (phenopromine sulphate), »skopyl» (methylscopolamine nitrate), and subcutaneous administration of fluids but continued to vomit. Became more and more lethargic, finally died. Autopsy revealed in addition to minimal subdural bleeding and incipient pneumonia a considerable enlargement of the adrenals (combined wt. 20 g), which had a peculiar, roughly granulated surface. Thymus smaller than normal (5 g). Microscopic examination (K. LINDBERG): »The cortices of the adrenals showed unusually marked convolutions and were also considerably wider than

[1] The author wishes to thank Dr. LINDBERG for carrying out the microscopic examination in this case and the next.

usual. The outer layers were fascicular in structure but showed no spongiocytes; like the inner, more irregularly constructed cortical layers they consisted of cells with sometimes darker, sometimes lighter cytoplasm. Around the centrally located medullary portions, which were of normal extent, a relatively thin layer of cortical cells in markedly reticular arrangement could be observed: evidently these were rests of the foetal cortex.» D.: adrenal hyperplasia.

Case 3. E.T. 605/48. Boy, brother of aforementioned patient. Mother healthy during pregnancy. B. May 1, 1948; delivery normal. Birth wt. 4 370 g. Condition good the first two weeks after birth, but the child failed to gain in spite of an abundance of milk and the fact that in the beginning he nursed well. At the age of fourteen days he began to refuse the breast and one week later to vomit, at first immediately after meals but a few days later even between meals. The vomiting was sometimes projectile. On a few occasions somewhat frequent, loose bowel motions. May 24 admitted to Medical Dept. Kronprinsessan Lovisa's Children's Hospital. Somewhat lethargic and dehydrated, colour slightly greyish. Considerable haemoconcentration (hgb. 20.6 g, RBC 5.1 mill., haematocrit 60 %, serum protein 10.8 %). For technical reasons the blood pressure could not be determined. Blood sugar normal. On the following day collapse, with peripheral coolness and spotty cyanosis. On the basis of the clinical picture and in view of the autopsy findings in the case of the brother, who had shown similar symptoms, an adrenal affection was suspected and the patient was treated with oxygen, stimulants, penicillin, saline and glucose intravenously, and desoxycorticosterone acetate (hereafter referred to as DCA). He improved rapidly but during the following weeks he required daily subcutaneous administration of saline fluids to avoid continued loss of weight and haemoconcentration. It was not until DCA and salt were supplied in adequate quantities that a marked improvement could be noted. This improvement was characterized by a rapid increase in weight and cessation of vomiting (compare Fig. 1). As time went on the effect of DCA and salt separately and together was studied. It was evident that DCA could be discontinued without giving rise to any distinct deterioration in the patient's general condition providing he was given salt. As Fig. 1 shows, salt alone was not sufficient to produce a satisfactory increase in weight, however. DCA alone could not prevent loss of weight and vomiting. Full compensation was obtained with a combination of 2 mg DCA and 2 g salt per day. To avoid daily injections treatment with DCA in crystalline suspension (Percorten crystules Ciba[1]) was attempted. A single 20 mg intramuscular injection was then sufficient to keep the patient free of symptoms and permit a

[1] The preparation was supplied through the courtesy of Ciba Produkter AB, Stockholm.

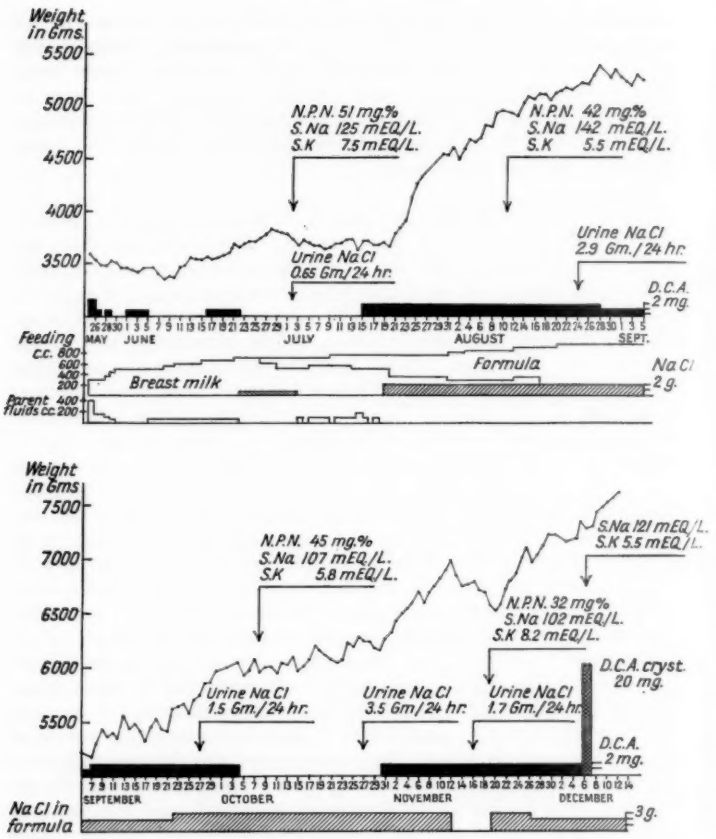

Fig. 1. Graphic record, Case 3.

normal increase in weight over a three week period, during which time the patient was sent home. The deterioration in general condition with vomiting and loss of weight which took place thereafter (see Table 1) has not been satisfactorily explained, since the patient was able earlier to go without DCA and the amount of salt given was not altered at any time. Even though no local signs of infection could be observed and the patient's temperature did not rise until after vomiting had begun, it seems most probable that he had acquired an infection which rendered

Table 1

Follow-up of Case 3.

Date	Weight in g	Clinical and Laboratory Findings	Treatment
1948			
Dec. 13	7 570	Gets along well; gains weight; no oedema; no pigmentations; genitalia normal; psychically fairly normal but doesn't sit alone; no teeth; discharged to home with advice to add 2.0 g table salt to formula.	2.0 g NaCl daily by mouth.
Dec. 21	7 730	Report: condition good; taking food well.	No change
Dec. 27		Report: appetite poor; begins to vomit.	No change
Dec. 29	7 300	Readmitted to hospital; vomiting, at times projectile; weight loss; colour slightly greyish; blood pressure 80 systolic; no haemoconcentration; hgb. 11.0 g, RBC 3.7 mill., WBC 19 600; diff. count: stabs 4, segmented 50, eosinophils 3, lymphocytes 42, monocytes 1 %; NPN 38 mg%; bicarbonate 20 mM/l; serum Na 104 meq./l; serum K 6.5 meq./l; serum chloride 95 meq./l.	No change
Dec. 31	7 150	Persistent vomiting and weight loss; fever 40° C; no local signs of infection.	Saline fluids subcutaneously; penicillin.
1949			
Jan. 3	7 300	Fever still unexplained; urine chlorides 2.3 g NaCl in 24 hrs; urinary 17-ketosteroids 14 mg in 24 hrs; genitals normal; bone age not advanced; height 70 cm.	No change
Jan. 5	7 160	Increased vomiting; temperature subfebrile.	2.0 mg DCA daily; otherwise no change.
Jan. 12	6 990	Vomits violently; slight haemoconcentration; serum Na 106 meq./l; serum K 5.9 meq./l; serum chloride 98 mM/l.	3.0 mg DCA daily; »skopyl» by mouth.
Jan. 14	7 110	Afebrile; vomiting ceases; weight loss stopped.	Parenteral fluids and penicillin discontinued; NaCl and DCA as before.
Jan. 18	7 480	Marked improvement; no vomiting; NPN 30 mg%; bicarbonate 20 mM/l; serum Na 117 meq./l; serum K 6.1 meq./l; serum chloride 109 meq./l.	No change
Jan. 20	7 550	General condition good; no oedema; another single injection of crystalline suspension of DCA given.	»Crystalline percorten» 30.0 mg; daily injections of DCA discontinued; 2.0 g NaCl per day as before.
Feb. 11	8 080	Gets along well; gains weight; no oedema; ECG normal; urinary 17-ketosteroids 10 mg in 24 hrs; still no signs of genital abnormalities; no pigmentations.	No change

the formerly adequate treatment inadequate. After having received another single dose of crystalline DCA he is now (Feb. 11, 1949) getting along well with only 2.0 g table salt added to the formula. At the age of nine months he still shows no macrogenitosomia and the skeletal age corresponds to the chronological. Throughout the whole period of observation, however, he has been excreting pathological amounts of urinary 17-ketosteroids (4 to 14 mg in 24 hrs). The laboratory findings in this case lend further support to the diagnosis of adrenal cortical insufficiency and are shown in Fig. 1 and Table 1. With the exception of the haemoconcentration in the first two weeks of hospitalization and an almost constant relative lymphocytosis the blood picture was normal. On one occasion the urine contained white blood cells indicating pyelonephritis. Intravenous pyelography revealed no abnormalities, however. Electrocardiograms were taken several times and were quite normal.

Discussion

Cases 1 and 2 resemble those described by DIJKHUIZEN and BEHR in every respect. They were not diagnosed during life, but there is no doubt that the clinical symptoms were due to adrenal insufficiency. In Case 3 the diagnosis of adrenal insufficiency was based on the typical clinical picture, the characteristic laboratory findings, and the obvious effect of specific treatment with desoxycorticosterone acetate and salt. Even though at over nine months of age the patient still shows no macrogenitosomia, there is doubtless congenital adrenal hyperplasia in this case also. This is indicated by both the autopsy findings in the case of the brother (Case 2), who showed almost identical clinical symptoms, and the constant excretion of pathological amounts of urinary 17-ketosteroids.

Summary

A short survey is given of a syndrome, described previously but still little known, consisting of congenital hyperplasia of the adrenal glands with adrenal cortical insufficiency with respect to water and electrolyte hormone and increased production of androgenic hormone. Three new cases are presented.[1]

[1] Since the preparation of this paper another case with this syndrome has been treated at K. L. C. H. (339/49).

Résumé

On fait un court exposé sur un syndrome, antérieurement décrit, mais encore peu connu, consistant en une hyperplasie congénitale des glandes surrénales, avec insuffisance de la substance corticale surrénale et production accrue d'hormones androgènes. On présente trois cas nouveaux.

Zusammenfassung

Der Verfasser gibt einen kurzen Überblick über ein Syndrom, das in der medizinischen Literatur früher beschrieben, aber wenig bekannt ist. Es besteht aus einer kongenitalen Hyperplasie der Nebennieren mit Nebennierenrindeninsuffizienz und vermehrter Absonderung von androgenem Hormon. Drei Fälle sind beschrieben.

Sumario

El autor expone brevemente un sindrome anteriormente descrito, pero todavía poco conocido, consistiendo en una hiperplasia congenita de las glandulas suprarrenales con insuficiencia de la corteza suprarrenal y un aumento de la producción de hormonas androgenas. Se exponen tres casos.

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Acrodynia and Mercury Poisoning

by

S. VAN CREVELD and M. M. P. PAULSSEN

In 1945 the idea came, quite accidentally, to WARKANY that acrodynia might be the consequence of mercury poisoning. Since then this possibility has been made to appear more probable by the closer observations of WARKANY in collaboration with HUBBARD (1) and of various other investigators (2, 3, 4, 5). In the urine of a number of cases of acrodynia a pathologically increased quantity of mercury could be demonstrated.

Moreover, it had already become evident that on several occasions the occurrence of symptoms of acrodynia was preceded by treatment with a vermifuge consisting of santonin and calomel, the external use of an unguent containing mercury (2, 3), or, as apparently frequently occurs in the U.S.A., the use of a mercury-containing »teething powder» to alleviate the pain of teething (5). In accordance with these facts, it had previously been found that the symptoms of acrodynia could be made to vanish by treatment with BAL (British Anti-Lewisite) (4, 5), which may be considered an antidote against mercury. Finally, in some fresh cases of acrodynia the hypersensitivity of the skin to mercury could be established by means of the patch test (3).

The questions now arise as to the extent to which the various aetiologies which in the course of years have been mentioned as responsible for the occurrence of solitary cases or epidemics of acrodynia must be laid aside, and whether we have always had to deal with a mercury poisoning, or with an allergy to mercury. Or the second question may be stated thus: to what extent may atypical morbid pictures, showing only some of the symptoms of acrodynia, be caused by mercury poisoning?

As regards the first question, it seems highly probable that mercury poisoning should be considered one of many causes of acrodynia. Already cases of acrodynia have been published in which no mercury could be found in the urine (see, among others, WARKANY and HUBBARD). Similarly, this substance has been found in the urine of children treated with mercury when symptoms of acrodynia were absent (1). Moreover, a picture resembling acrodynia sometimes occurs as a consequence of chronic arsenic poisoning. The other aetiologic factors in acrodynia which have been mentioned in the course of the years should be revised, however.

When the use of mercury is held responsible for the occurrence of symptoms of acrodynia, we have to bear in mind that in children morbid symptoms quite different from the picture of acute mercury poisoning may arise after the use of mercury. These symptoms, as well as those of acrodynia, are usually explained by assuming a special sensitivity to mercury. In this connection we should like to draw attention to the morbid pictures which have been described after the use of unguents with mercury (6) as well as to the so-called calomel disease which occurs especially in infants (7, 8) and is characterized by morbilliform and scarlatiniform exanthemata, swelling of the spleen, general swelling of the lymph glands, and, in the blood, by leukopenia and eosinophilia. After recovery, the patient's skin maintains a grey-brown discolouration for quite a while.

As to the aforementioned second question whether atypical morbid pictures showing only some of the symptoms of acrodynia may be caused by mercury poisoning, the following case will be of interest.

H., a boy nineteen months old, complained about his feet in the middle of August 1948. The paediatrician, Dr. W. A. M. Weyers, could not find anything abnormal, especially any redness of the feet or nose; however, the hands were red. There was no exanthema or scaling of the skin. The urine was normal. The pulse rate was 90 p.m. and the blood pressure 100/70 mm Hg. Dr. Weyers considered the diagnosis acrodynia, but almost all points of contact were lacking.

As the condition of the child grew worse, he was admitted to a hospital on August 30. There also nothing in particular could be found by

Dr. W., but the child still complained of pain in the feet. However, the possibility of a psychical factor could not be excluded. The boy's intelligence was excellent. He was discharged from the hospital in good condition on September 4.

On September 15 Dr. W. reexamined the child; distinct miliaria was now present and the hands and feet were red and clammy. The pulse rate had risen to 130 and the blood pressure was 110/70 mm Hg. The child was fretful and had not eaten during the previous days; he had lost flesh. Though the picture was not characteristic, acrodynia was again suspected. As the condition did not ameliorate, the child came to us during Dr. W.'s holidays.

He was a weak, thin, hypotonic boy, without anaemia. Eyes, ears, throat, heart, lungs, and abdomen appeared normal. The spleen was scarcely palpable. The external genitals were normal. The extremities, with the exception of the hands and feet, were also normal, as well as the reflexes. The hands and feet were cold, clammy, and red, especially the dorsal aspect of the fingers. The pulse was frequent and regular; the blood pressure was normal.

In the urine there were no abnormalities. The morphological blood picture showed 9 600 leukocytes. Differential count: polymorphonuclear leukoc. 39; band forms 1; lymphoc. 51; monoc. 8; eosinophilic 1.

The skin of the abdomen, the lower part of the back, and the dorsal aspects of hands and feet showed an exanthema of non-specific character.

The case history revealed that a maternal uncle suffered from bronchial asthma.

We were also of the opinion that the symptoms somewhat resembled acrodynia, though this morbid picture was by no means complete. In connection with the facts mentioned in the beginning of this article we enquired whether the child had recently received any drugs. It now appeared that two and three months before, respectively, he had received santonin and calomel powders (25 mg santonin and 50 mg calomel in each powder) twice daily for three successive days; the father had ordered these and subsequently administered them again after the first cure. So it became necessary to examine the urine for the presence of mercury. This first examination was performed in the State Institute for Public Health in Utrecht; the significant quantity of 280 γ mercury per liter was found.

As we now desired to treat the child with BAL, controlling the excretion or mercury in the urine, he was taken, with Dr. W.'s approval, into the Paediatric Clinic of the University of Amsterdam. There we saw again the pale, thin boy with sunken eyes. On the breast and abdomen (from the armpits to below the umbilicus) many small red elevations were noted, some with small blisters (Fig. 1). The same condition was found on the lower part of the back, on the front, scattered over the face, and on the dorsal aspects of the hands. The exanthema resembled miliaria most closely; Prof. Prakken, the dermatologist, agreed

that it was not at all like mercury exanthema. The skin of the hands and feet was somewhat scaly and the hands and feet were clammy. The pulse rate was 200, regular and equal. The liver was scarcely palpable. The urine and faeces were normal. The ECG was normal.

In administering BAL we gave the dosage indicated by ELMORE (5). To determine the quantity of mercury excreted the urine was regularly collected in a receptacle free from heavy metals. BAL (dimercaprol) was administered intramuscularly, first twelve injections of 2.5 mg/kg every four hours, then every six hours for two days, and finally twice a day for eight days, for a total of twelve days. Preceding each injection 0.5 cc of 2 % procaine solution was injected locally. The preparation used was a 10 % solution of BAL in ol. arachidis with 20 % benzylbenzoate. These injections had no harmful effect either locally or on the general condition.

With regard to the determination of the mercury in the urine, the following may be observed. To obtain chemical control of treatment with 2.3 dimercapto-propanol (dimercaprol, BAL) during the whole course of recovery in a case of mercury poisoning, it is necessary to employ a method which may be put into practice more easily than the methods commonly used. Therefore we performed the determinations in accordance with KOZELKA's method (9). In this way determinations could be performed twice daily. Moreover, this method required much smaller quantities of urine than the older methods.

The principle of the method is in brief as follows. 25—100 cc of urine, depending on the amount of mercury to be expected, is treated in a mixture of sulfuric acid, sulfate of copper, and sulfate of ammonium in such a way that any volatilizing-mercury present is gathered. Then the remaining mercury is distilled by means of a twenty-minute stream of chlor; any excess chlor is removed by gaseous sulfur dioxide. The distillate obtained in this way is brought to pH 1 by means of thymol blue and the mercury is shaken out with dithizon in tetrachlormethane. The excess of dithizon and any contaminative copper dithizonate are removed by means of 9 N. ammonia. The intensity of the red-brown colour of the mercuric dithizonate in the tetrachlormethane

Fig. 1. Condition of skin on breast and abdomen on admission.

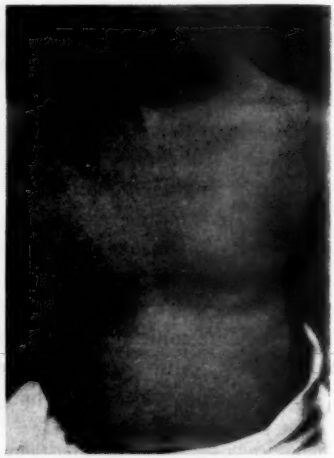

Fig. 2. Condition of skin on breast and abdomen 8 days after beginning of BAL treatment.

is measured in a photometer, and the value thus obtained in a control curve indicates the quantities of mercury present in the sample under examination.

The results obtained in our patient were the following:

Day	Quantity of Urine in 24 hrs. in cc	Quantity of Mercury Present in This Urine in γ	Quantity of Mercury per Liter Urine in γ	
Sept. 30	210	76	360	← BAL
Oct. 1	220	88	400	
2	290	70	240	
3	285	29	100	
4	260	16	60	
5	230	9	38	
6	220	8	36	
7	215	8	37	
8	145	7	49	
9	60	4.5	75	
10	95	4.3	45	
11	145	4.1	28	
12	215	2.2	10	← BAL is
13	260	3.9	15	stopped

Examining twenty children with acrodynia, WARKANY and HUBBARD found mercury in the urine of eighteen; in fifteen more than 50 γ per liter and in ten quantities varying between 100 and 400 γ per liter. The two children whose urine did not contain mercury were eight and fourteen years old, respectively — unusually advanced ages to incur acrodynia. In forty nine control children they found more than 50 γ of mercury in the urine of only one and it appeared that this child had received calomel. In the majority of the control children far less than 50 γ per liter was found. We found in one control child only a few γ of mercury per liter urine.

From the very day on which the BAL therapy was started we found, as other authors have also done, a surprising amelioration of the condition. The exanthema on the abdomen and back quickly disappeared (Fig. 2); the hands and feet regained their normal colour and were no longer cold and clammy; the general condition of the child rapidly improved. The pulse rate decreased within a few days to normal. At the end of the BAL treatment the skin was quite normal, with the exception of some scaling on soles, palms, and knees which had appeared during the treatment without preceding perspiration and which had gradually disappeared. Moreover, it was remarkable that the blood showed a temporary eosinophilia (6 %).

The excretion of mercury in the urine, already very high before the BAL treatment, increased somewhat in the beginning but then diminished rapidly and steadily. The general opinion is that in severe cases of poisoning with heavy metals the first days of BAL application cause increased excretion in the urine. On this point we have only few data, most of which apply to experimentally and clinically acute cases of mercury poisoning (10, 11, 12). These control animals and adult persons were all treated with BAL within some hours or days after Hg poisoning generally followed by the beginning of excretion of Hg in the urine. In acrodynia caused by mercury poisoning, both the communicated cases and our own one, the mercury was applied a considerable time before the clinical symptoms appeared.

In such cases the excretion of Hg in the urine under the in-

fluence of BAL has been determined by ELMORE, among others. He found 80 γ per liter in the beginning in a seven and a half month old girl with symptoms of acrodynia following application of calomel, after some days 60 γ per liter, and still later 120 γ per liter. In a second patient, a boy ten months old, the values were resp. 400, 170, and 140 γ per liter. Thus in the first child a decrease was noticed in the beginning, followed by an increase, while the second child had first a high excretion followed by a rapid decrease. (The values in control cases were always smaller than 4 γ per liter.)

By means of a not very sensitive method, BIVINGS and LEWIS found in their patient, a girl six months of age, 100 γ mercury per 100 cc urine before the BAL treatment. Nine days after the commencement of BAL therapy 60 γ per 100 cc urine were found, and ten days later mercury was totally absent from the urine.

In three cases which were not treated WARKANY[1] found that in one the mercury disappeared from the urine within two months, while the second patient still excreted mercury in the urine after two months and the third patient even after four months.

From the results obtained in one case we may not draw conclusions too quickly. It seems that the excretion of mercury in our case was already at its maximum and that the application of BAL stimulated the excretion at the same time that amelioration of the clinical condition occurred. The opinion of DANIELLI AND CO-WORKERS (13) that the almost non-toxic Hg-BAL-complex is present in the body in an extracellular condition and that this complex gradually leaves the body would explain the quick recovery of the child and at the same time the rapid decrease of the quantity of mercury in the urine. Similarly, it appears that when we stopped the BAL therapy and then after a few days examined a twenty four hour specimen of urine again, we found an even higher value, viz. 12.4 γ in 150 cc urine, i.e. 69 γ per liter.

We examined the faeces for mercury only at the end of the BAL treatment, with negative results.

[1] Personal communication to BIVINGS and LEWIS (4).

Summary

This article describes an atypical case of acrodynia which was apparently caused by the use of calomel. During treatment with BAL the symptoms disappeared very quickly and after a temporary increase the enlarged excretion of mercury soon diminished.

October 1948.

Résumé

Acrodynie et empoisonnement par mercure

Description d'un cas atypique d'acrodynie qui parut avoir été causé par l'usage de calomel. Au cours du traitement par BAL, les symptômes disparurent très rapidement; l'élimination accrue de mercure, après une augmentation temporaire, ne tarda pas à diminuer.

Zusammenfassung

Akrodynie und Quecksilbervergiftung

Ein atypischer Fall von Akrodynie wird beschrieben, der anscheinend durch die Verwendung von Kalomel verursacht war. Während einer Behandlung mit BAL verschwanden die Symptome sehr bald; nachdem die vermehrte Absonderung von Quecksilber eine Zeit hindurch zunahm, ging sie bald zurück.

Sumario

Acrodynia y intoxicación por el mercurio

Descripción de un caso atipico de acrodynia, al parecer producido por el uso de Calomel. En el curso del tratamiento con BAL, los sintomas desaparecieron rapidamente; la excreción de mercurio aumentada, luego de un ascenso temporal, disminuye rapidamente.

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Fettleibigkeit und Diabetes

von

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Einleitung

Seit langem besteht die Vorstellung, dass fettleibige Personen verhältnismässig oft an Diabetes erkranken, was auch durch völlig zufriedenstellende statistische Untersuchungen nachgewiesen werden konnte. Dieser Umstand wurde durch die Annahme erklärt, dass Personen, die viel Fett essen und deswegen fettleibig werden, ihre Bauchspeicheldrüse schädigen, so dass diese frühzeitig versagt. Theoretisch könnte man erwarten, dass Personen, die reichlich Kohlehydrate zu sich nehmen, ihre Bauchspeicheldrüse anstrengen und deswegen an Diabetes erkranken, während eine Diät, die reich an Fett ist, eigentlich einen gewissen Schutz gegen Diabetes gewährt. Würde eine Diät, die zum überwiegenden Teil aus Fett besteht in der Tat Diabetes verursachen bzw. diese Krankheit verschlechtern, so hätte man früher Diabetiker in einer Weise behandelt, die zur Verschlechterung und zum Fortschreiten ihrer Krankheit geführt hat. Da man aber zu jener Zeit kein Insulin zur Verfügung hatte, war die Behandlungsmethode gewissermassen durch die Art der Krankheit diktiert. Im allgemeinen kann man ferner sagen, dass eine Verbesserung des Lebensstandardes dazu führt, dass mehr Fett konsumiert wird. Eine Verbesserung des Lebensstandardes würde man also mit einem erhöhten Risiko für Diabetes bezahlen. Das Problem Fettleibigkeit und Diabetes ist mit anderen Worten sehr bedeutungsvoll. Es wurde versucht den Zusammenhang zwischen Fettleibigkeit und Diabetes einerseits mit Hilfe von Tierversuchen und andererseits durch statistische Analyse von Zahlenangaben, die

sich hauptsächlich an die Diabetesmortalität beziehen, klarzustellen. Die letztgenannten Fragen sollen hier zuerst diskutiert werden.

Im Sinne der oben genannten Theorie sollte bei einer fettreichen Diät die Anzahl Erkrankungen an Diabetes zunehmen, während sie bei einer an Kohlehydrat und Eiweiss reicheren Diät abnehmen sollte. Mit anderen Worten sollte man eine Verminderung der Frequenz an Diabetes unter Kriegsperioden mit Lebensmittelrationierung erhalten.

Die Frequenz der Neuerkrankungen an Diabetes

Über die Frequenz der Neuerkrankungen an Diabetes existieren keine zuverlässigen statistischen Angaben. Man könnte sich theoretisch vorstellen, dass man innerhalb einer bestimmten Population Angaben über die Anzahl Personen, welche jährlich das erste Mal einen Arzt besuchen, einsammeln und dabei Frequenzziffern erhalten würde, die mit der Anzahl der Neuerkrankungen einigermassen übereinstimmen dürften. Diese Werte wären natürlich nicht vollständig exakt, da man ja nicht weiss, wie lange der betreffende krank gewesen ist, bevor er sich an den Arzt gewandt hat; ausserdem kann man ja natürlich nicht die Fälle erfassen, die sich niemals an einen Arzt wenden. Es ist indessen kaum von Interesse diese Möglichkeiten zu besprechen, da ja keine derartigen Zahlenangaben vorliegen.

Diabetesfrequenz

Es ist während der Kriegsjahre möglich gewesen Angaben über die Anzahl Diabetiker in der Bevölkerung zu erhalten. Nachdem während des zweiten Weltkrieges eine Lebensmittelrationierung notwendig war, erhielten Diabetiker im allgemeinen eine Extrazuteilung von Lebensmitteln. Aus diesem Grunde wandte sich die grosse Mehrzahl von Diabetikern an die staatlichen Stellen, welche die Rationierung unter sich hatten, wodurch sich die Möglichkeit ergab, Angaben über ihre Anzahl zu erhalten. Diese Möglichkeit wurde in Schweden und in der Schweiz

ausgenützt. Die Angaben in Schweden wurden dank der Initiative von A. LICHTENSTEIN gesammelt und in einer Arbeit von DAHLBERG, JORPES, KALLNER und LICHTENSTEIN 1947 veröffentlicht. Es ergab sich, dass die Diabetesfrequenz in den verschiedenen Altersklassen verschieden hoch ist. In den jüngeren Altersklassen kam Diabetes nicht so häufig vor, aber ungefähr mit dem 40. Lebensjahr beginnt seine Frequenz zuzunehmen, und zwar sowohl bei Frauen als auch bei Männern (die Diabetesfrequenz ist im Alter von 65—70 Jahren ungefähr 5—6 mal so gross als im Alter von 35—40 Jahren). Ausserdem ergab sich, dass Diabetes häufiger in grösseren Städten als in kleineren vorkommt und am spärlichsten bei der Landbevölkerung auftritt.

Die Anzahl der erfassten Diabetesfälle muss nun von verschiedenen Umständen abhängig sein: 1. in welchem Ausmasse die Krankheit festgestellt wird, 2. wie lange der Kranke nach Beginn der Krankheit lebt und 3. davon in welchem Ausmasse die Kranken die Möglichkeit eine Extralebensmittelzuteilung zu erhalten, ausnützen. Natürlich wird die Landbevölkerung von der Lebensmittelrationierung weit geringer berührt als die Stadtbevölkerung. Auf dem Lande ist die Extrazuteilung ganz einfach nicht in gleichem Ausmasse notwendig. Aus diesem Grunde ist es natürlich, dass die ermittelte Krankheitsfrequenz der Dörfer geringer ist. Dies dürfte ausserdem auch darauf beruhen, dass die Krankheit unter der Landbevölkerung in geringerem Ausmasse als bei den Stadtbewohnern bekannt wird. Auf den Dörfern ist ja die Möglichkeit einen Arzt zu besuchen geringer, u. s. w. Dass die Krankheitsfrequenz mit dem Alter zunimmt ist auch natürlich, nachdem das Todesrisiko für jüngere Personen jetzt nicht mehr so gross ist; sie sind mit anderen Worten bis hinauf in das höhere Alter am Leben. Es dürfte aber nicht wahrscheinlich sein, dass die Zunahme in höherem Alter nur auf dieser Akkumulation beruht. Es liegt die Vermutung nahe, dass die starke Frequenzzunahme in höherem Alter wenigstens zum Teil auf einem Zusammenhang zwischen Arteriosklerose und Diabetes beruht. Auf diese Frage soll hier nicht näher eingegangen werden, es soll nur darauf hingewiesen werden. Auf dieses Problem soll evt. in einer späteren Arbeit eingegangen werden.

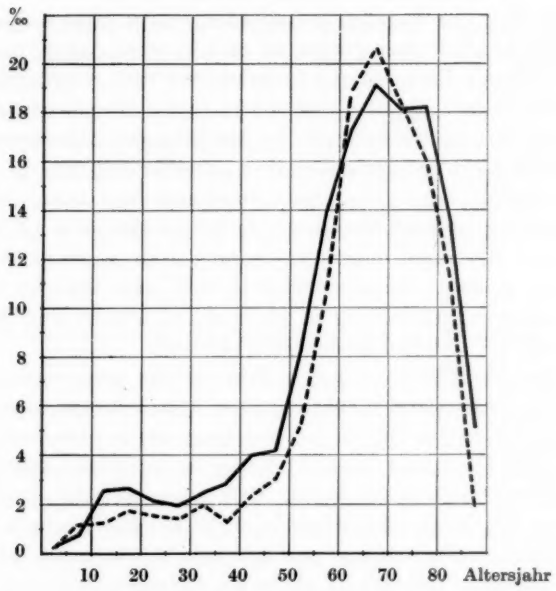

Abb. 1. Frequenz von an Diabetes Erkrankten in verschiedenen Altersgruppen in Stockholm.

----- Männer. ——— Frauen.

Um die Diabetesfrequenz in verschiedenen Altern zu beleuchten, soll ein Diagramm über die Verhältnisse in Stockholm wiedergegeben werden. Wir haben uns nämlich bemüht über die Verhältnisse in dieser Stadt so vollständige Angaben als möglich zu erhalten. (Abb. 1.)

Unter der Annahme von zwei Populationen mit dem gleichen Diabetesrisiko in den verschiedenen Altersgruppen, aber mit verschiedener Altersverteilung, ergibt sich aus dem Diagramm, dass die Diabetesfrequenz in diesen beiden Populationen verschieden ist. Solche zahlenmässige Angaben über die Diabetesfrequenz in Populationen als Ganzheit müssen deswegen mit einem gewissen Misstrauen betrachtet werden. Streng genommen sind sie nicht ohne weiteres mit einander zu vergleichen.

Tab. 1

Anzahl Zuckerkranke per 1 000 Untersuchte bei Militäruntersuchungen in den Jahren 1942—1946.

Jahr	‰ Diabetiker bei den Untersuchten
1942	2,41
1943	2,24
1944	2,59
1945	2,24
1946	2,48
1942—46	2,39

In der offiziellen Statistik finden sich in den letzteren Jahren (seit 1942) zahlenmässige Angaben über die Diabetiker unter den in den Militärdienst Einberufenen, die in der Tabelle 1 weiter oben wiedergegeben werden. Es ergibt sich, dass die Diabetesfrequenz sich im 20. Lebensjahr um ungefähr 2.5 % hält. Dass die Werte für die verschiedenen Jahre verschieden sind, dürfte auf Zufallsmomenten beruhen. Die angeführten Werte stimmen mit unseren Werten für die 20—25-Jährigen in Stockholm überein. Man darf annehmen, dass Männer, wenn es sich darum handelt den Militärdienst zu machen um später das Vaterland zu verteidigen, gewissenhaft alle Krankheiten angeben, die evt. zu einer Befreiung vom Militärdienst führen. Deswegen dürften die von den Einberufenen erhaltenen zahlenmässigen Angaben ziemlich korrekt sein, und dies um so mehr, da ja alle Einberufenen von Ärzten untersucht werden. Die Steigerung, welche die Werte für Männer im Alter von 20—25 Jahre zu erreichen scheinen, dürfte gerade auf die erhöhte Anzahl von Diabetesfällen im Alter von 20—21 Jahren, welche durch die in den Militärdienst Einberufenen bedingt werden, beruhen. Eine entsprechende Steigerung für Frauen ist nicht vorhanden.

Für die Schweiz konnte ich keine entsprechende Altersverteilung von Diabetikern, die eine Extralebensmittelzuteilung erhalten haben, vorfinden. Fleisch (1947 a und 1947 b) hat die

zahlenmässigen Angaben für die einzelnen Kantone vom Korrelationsgesichtspunkt aus einer Bearbeitung unterworfen.

Wir wollen die Arbeit von FLEISCH in Kürze besprechen. Er konnte zeigen, dass zwischen der Diabetesfrequenz in den verschiedenen Kantonen einerseits und dem Wehropferbeitrage, bzw. dem Reinvermögen per Person und der Prämienbezahlung für Lebensversicherungen andererseits, eine sehr starke Korrelation vorliegt. Diese Korrelationswerte betragen 0.9 und sind mit anderen Worten, weit grösser als die, welche man im allgemeinen findet, wenn es sich um biologische Verhältnisse handelt, was FLEISCH selbst hervorhebt. FLEISCH gibt leider keine Primärwerte an, weswegen seine Berechnungen nicht kontrolliert werden können. Diese sind aber wahrscheinlich richtig, nachdem FLEISCH selbst die Korrelationen als hoch und etwas unwahrscheinlich angesehen hat und seine zahlenmässigen Angaben sicher sorgfältig kontrolliert hat. Er ist im übrigen der Ansicht feststellen zu können,

1) dass die Diabetesfrequenz mit dem Wohlstand zunimmt,
2) dass je mehr intellektuelle Arbeiter in einem Kanton vorhanden sind, desto mehr Diabetiker finden sich in ihm,
3) dass je mehr Personen sich der Landwirtschaft widmen, desto geringer ist die Anzahl Diabetiker,
4) dass je mehr Extralebensmittelzuteilungen für andere Krankheiten gegeben werden, desto grösser ist die Anzahl Diabetiker.

Auf Grund des letztgenannten Umstandes bespricht der Autor in welchem Ausmasse die Korrelation darauf beruhen kann, dass die Landbevölkerung nicht so oft bei Krankheit eine Extrazuteilung begehrt. Er berechnet aus diesem Anlass partielle Korrelationen und ist der Ansicht ausschliessen zu können, dass das letztgenannte Verhalten eine grössere Rolle spielen kann. Er glaubt wirklich einen Zusammenhang zwischen Diabetes und Lebensstandard festgestellt haben zu können. Es besteht aber Anlass sich dieser Folgerung sehr kritisch gegenüber zu stellen. Nehmen wir die Korrelation mit den Versicherungsprämien zum Ausgangspunkt. Es ist klar, dass wenn die Summe der Versicherungsprämien steigt, so bedeutet dies im grossen und ganzen,

dass die Anzahl, die Versicherungen abschliesst, grösser ist. Schliesst man eine Versicherung ab muss man im allgemeinen von einem Arzt untersucht werden, wobei ein Teil der Diabetesfälle entdeckt wird. In derartigen Fällen wird die Versicherung verweigert oder nur gegen erhöhte Prämien abgeschlossen. Es ist also klar, dass falls die Summe der Versicherungsprämien steigt, so muss die Anzahl der Diabetiker zunehmen, weil die Krankheit öfters entdeckt wird. Ausserdem kann man davon ausgehen, dass eine Bevölkerung, die auf einem höheren Lebensstandard lebt, sich eher leisten kann Versicherungen einzugehen als andere. Es ist also klar, dass eine Korrelation zwischen der Summe an Versicherungsprämien und Diabetes wenigstens zum Teil auf die ärztliche Untersuchung zurückzuführen ist. Handelt es sich um die Korrelation zwischen Höhe der Steuer und Diabetes, so muss berücksichtigt werden, dass die Angaben ziemlich unsicher sind. Die Steuerhöhe ist ein indirektes Mass für den Wohlstand, wird aber auch durch die Ehrlichkeit der Bevölkerung, um die es sich handelt, bedingt und durch die Häufigkeit, wie oft in ihr falsche Steuererklärungen abgegeben werden. Es ist absurd anzunehmen, dass ein direkter Zusammenhang zwischen hohem Einkommen und Diabetes vorliegt, wie FLEISCH das betont. Einkommen an und für sich kann ja keine Krankheit verursachen. Ebenso unangebracht ist es einen Zusammenhang zwischen Diabetesfrequenz und Ehrlichkeit der Bevölkerung anzunehmen. Die Ursache der Korrelation muss anderswo gesucht werden. Man kann davon ausgehen, dass Vermögene öfters den Arzt suchen und Zugang zu Ärzten haben und dass dies in gewissem Masse eine Korrelation zwischen hohem Einkommen und Diabetes bedingen kann.

Ein anderer Faktor, der auch beachtet werden muss ist, dass Diabetes entschieden häufiger in den höheren Altersgruppen vorkommt. Die Personen, die ein höheres Einkommen und Wohlstand erreicht haben, sind natürlich nicht so oft jung. Erst wenn man älter wird, erhält man ein höheres Einkommen oder erbt ein Vermögen.

Unter solchen Verhältnissen besteht Anlass, dass die Annahme eines direkten Zusammenhanges zwischen Wohlstand und Diabetes von FLEISCH unbewiesen ist. Es ist im übrigen klar, dass

FLEISCH hierbei nicht an einen direkten Zusammenhang denken kann, sondern dass ein dritter Faktor eine Rolle spielen muss. Man kann vermuten, dass er sich vorstellt, dass dieser dritte Faktor in einem erhöhten Fettverbrauch bei höherem Lebensstandard besteht, obwohl er dies in seiner Arbeit nicht sagt.

Zusammenfassend kann man behaupten, dass die zahlenmässigen Angaben von FLEISCH nicht ausreichend beweisend sind um positive Schlüsse aus ihnen zu ziehen.

Diabetesmortalität

Da man also keine direkten Angaben zur Verfügung gehabt hat, hat man versucht die Diabetesmortalität dazu anzuwenden ein Mass für die Diabetesfrequenz zu erhalten. Man scheint aber nicht diskutiert zu haben, in welchem Grade ein solches Vorgehen erlaubt ist. Wir wollen auf jeden Fall ausführlicher als gewöhnlich diese Frage berühren.

Unter der Voraussetzung, dass alle, die von einer bestimmten Krankheit betroffen werden, auch an dieser sterben, kann man die Mortalität als Mass für die Krankheitsfrequenz anwenden. Lebt der Betreffende eine kürzere oder längere Zeit nachdem er von der Krankheit betroffen wurde, so wird die Mortalität natürlich entsprechend der mittleren Krankheitszeit hinausgeschoben. Aus diesen Gesichtspunkten kann man Krebs mit tödlichem Ausgang als einen ungefähren Ausdruck für die Erkrankungsfrequenz an dieser Krankheit ansehen. Die Anzahl der Fälle, die nach einer Behandlung gesund werden, ist nämlich sehr gering und kann unberücksichtigt bleiben, wenn man über die Frequenz des Krebses eine ungefähre Vorstellung erhalten will. Will man exaktere Angaben erhalten, muss man versuchen zu berücksichtigen, dass die Behandlung dazu führt, dass eine geringere Anzahl gesund wird. Es ist praktisch unmöglich eine Korrektion dieses Verhaltens auszuführen.

Ganz anders verhält es sich mit einer Krankheit wie Diabetes. Vor allem ist das Intervall zwischen Krankheit und Tod ziemlich gross. Deswegen sterben viele an anderen völlig beziehungslosen Krankheiten, wie Unglücksfall. Ferner werden viele Todesfälle

durch Krankheiten verursacht, die einen gewissen Zusammenhang mit Diabetes haben, z. B. Lungenentzündung. Der Zusammenhang zwischen solchen Krankheiten ist aber nicht absolut. Im Einzelfall ist es unerhört schwer, um nicht zu sagen unmöglich, zu entscheiden, ob die Lungenentzündung durch den Diabetes verursacht wurde oder auch unabhängig von dieser Krankheit eingetroffen wäre.

Die Ärzte sind aber geneigt Diabetes als Todesursache auch in solchen zweifelhafteren Fällen anzugeben. Hieraus ergibt sich, dass die Mortalität für Diabetes, die man erhält, grösser ist als sie sein dürfte, aber doch keinesfalls alle Todesfälle bei Personen, die an Diabetes leiden, umfasst. Ein deutliches Beispiel hierfür ist, dass wenn die Mortalität abnimmt, z. B. auf Grund von Insulinbehandlung, doch keine bestehende Verminderung zustandekommt. Nach einer Zeit steigt die Mortalität wieder an. Die Insulinbehandlung bedingt, dass die Diabetiker älter werden, führt aber nicht dazu, dass die Anzahl derer, als deren Todesursache Diabetes angesehen wird, abnimmt, wenn der Prozess Zeit gehabt hat sich zu stabilisieren. Die Insulinbehandlung führt eher zu einem entgegengesetzten Effekt und führt zu einer erhöhten Mortalität, da eine grössere Anzahl von Personen ärztliche Hilfe sucht, wenn es bekannt wird, dass diese effektiv ist. Hierdurch werden mehr Diabetesfälle von Ärzten festgestellt. Überhaupt beruht die Anzahl Diabetesfälle in hohem Grade darauf, in welcher Ausdehnung das Vorkommen von Diabetes den Ärzten bekannt ist. Die Todesfälle an Diabetes werden also unter wohlsituierten Patienten weit zahlreicher, da diese in grösserem Ausmasse wissen wie wichtig es ist ärztliche Hilfe zu suchen und diese auch in Anspruch nehmen. Sterben solche Personen später, so geben die Ärzte Diabetes als Todesursache verhältnismässig oft an. Handelt es sich um arme Personen, die den Arzt nicht so oft wegen solcher vagen Symptome aufsuchen, können die Ärzte nicht im gleichen Ausmasse Diabetes als Todesursache angeben. Liegen die Verhältnisse derart, so kann man erwarten, dass die Diabetesmortalität mit steigendem Lebensstandard zunimmt, und besonders, dass die Diabetesmortalität in den wohlsituierten Gesellschaftsklassen besonders hoch ist.

HIMSWORTH hat die Frage Diabetesmortalität und Diät am eingehendsten bearbeitet. Aus diesem Grunde soll seine 1935 erschienene Arbeit besprochen werden. HIMSWORTH führt erst die Tatsache an, dass die Diabetesmortalität in zahlreichen Ländern bis zur Jetztzeit angestiegen ist; als Ursache dafür glaubt er den Umstand ansehen zu dürfen, dass man jetzt mehr Fett verzehrt als früher. Indessen muss man in erster Linie daran denken, dass die Zunahme der Diabetesmortalität auf einer vollständigeren Registrierung derselben oder auf einem anderen zufälligen Faktor beruhen kann. Die offizielle Mortalitätsstatistik wird ja im allgemeinen immer besser im Laufe der Jahre. Ferner haben unsere diagnostischen Möglichkeiten Diabetes festzustellen nicht unwesentlich zugenommen und dies vor allem, wenn man berücksichtigt, dass die Anzahl der Ärzte zugenommen hat. Das wichtigste ist aber, dass die Lebenslänge, und besonders die der Diabetiker, zugenommen hat, aber auch, dass die Alterszusammensetzung der Bevölkerung eine Veränderung erfahren hat. Es ist klar, dass diese Veränderungen eine grosse Wirkung haben müssen. Aus der weiter oben wiedergegebenen Kurve für Diabetiker in Schweden ergibt sich, dass die Anzahl Diabetiker in den höheren Altersgruppen wesentlich grösser ist. Eine Verschiebung der Alterszusammensetzung der Bevölkerung gegen das höhere Alter muss, ebenso wie die verminderte Anzahl von Kindern, zu einer erhöhten Diabetesmortalität führen. Eine solche Verschiebung kann völlig ausreichend sein um die vermehrte Diabetesmortalität zu erklären. HIMSWORTH bespricht diese Möglichkeiten nicht, sondern begnügt sich damit hervorzuheben, dass eine verschiedene berufliche Geschicklichkeit der Ärzte keine Erklärung für die Verschiedenheiten sein kann.

Die herabgesetzte Diabetesmortalität während des letzten Teiles des ersten Weltkrieges weist in gewisser Hinsicht darauf hin, dass eine knappe Kost für Diabetiker vorteilhaft ist. Die herabgesetzte Mortalität kann kaum darauf beruhen, dass die Erkrankungsfrequenz bei knapperer Diät herabgesetzt wird. In diesem Falle dürfte sich der Effekt erst viel später geltend machen. Ein herabgesetztes Erkrankungsrisiko macht sich in den Mortalitätswerten erst etwa ein Jahrzehnt später geltend.

HIMSWORTH diskutiert ferner den Mortalitätsunterschied zwischen Stadt- und Landbevölkerung und findet für England und Wales, dass die Mortalität der Landbevölkerung höher ist. Entgegengesetzt liegen die Verhältnisse in Amerika. Erst in diesem Zusammenhang bespricht HIMSWORTH die Bedeutung der Altersverteilung und hebt hervor, dass man die Zahlenangaben für England und Wales nicht ohne weiters mit denen für Amerika vergleichen kann. Es muss eine Korrektion für die Altersunterschiede vorgenommen werden. Nimmt man diese vor, so verschwinden die Unterschiede. HIMSWORTH selbst legt bei der Untersuchung der Diabetesmortalität in den verschiedenen Gesellschaftsklassen nicht diesen Gesichtspunkt zugrunde und korrigiert die Werte nicht unter Berücksichtigung der Altersverschiedenheiten.

Zusammenfassend dürfte festgestellt werden, dass man auf Grund der offiziellen Statistik nichts beweisen kann, wenn man nicht die Altersverschiedenheiten berücksichtigt. Es ist im übrigen unmöglich bestimmte Schlüsse über evt. Unterschiede zu ziehen, u. a. im Hinblick auf den bereits erwähnten Umstand, dass unsere mangelhafte Kenntnis über früheren Diabetes die Mortalitätswerte in einem schwer zu bestimmenden Ausmasse beeinflusst.

Vor und nach der Veröffentlichung der Arbeit von HIMSWORTH haben zahlreiche Autoren ähnliche Gesichtspunkte angeführt. Gegen alle kann eine Kritik von prinzipiell derselben Art, wie hier bereits angeführt, gerichtet werden. Soweit uns bekannt, stellt in dieser Hinsicht die Arbeit von SCHMIDT und SAUERMANN (1944) eine Ausnahme dar. Diese Autoren haben durch spezielle Untersuchungen gezeigt, dass der Mortalitätsunterschied zwischen den verschiedenen Gesellschaftsklassen durch Altersverschiedenheiten bedingt wird. Die bei Arbeitern ungefähr 50 % niedrigere Mortalität ist allein auf diese zurückzuführen. Die Autoren versuchen aber das Risiko an Diabetes zu erkranken unter Anwendung eines äusserst approximativen Vorgehens zu berechnen. Die zahlenmässigen Angaben sind aber so unsicher, dass ihnen u. a. weil die Autoren die Altersverschiedenheiten beim Erkrankungsrisiko nicht berücksichtigen konnten, sondern auf die Annahme bauen,

dass das Erkrankungsrisiko sich parallel mit dem Alter ändert, was sicher nicht stimmen dürfte, kein Wert zugemessen werden kann.

Diabetes unter Berücksichtigung der Rasse

In diesem Zusammenhang soll hervorgehoben werden, dass die allgemein angeführte Behauptung, dass Juden besonders oft an Diabetes leiden, als völlig unbegründet angesehen werden muss. Die Annahme gründet sich auf Mortalitätswerte, die nicht beweisend sind. Es hat sich auch ergeben, dass die hohen Mortalitätswerte verschwinden, wenn man die Verteilung des Materiales auf die verschiedenen Gesellschaftsklassen und Alter berücksichtigt; vgl. z. B. BIENECK (1940). Die hohen Werte für Juden werden ganz einfach dadurch bedingt, dass man hauptsächlich Material aus den wohlsituierten Gesellschaftsklassen und mit einem höheren Durchschnittsalter untersucht hat. Dasselbe gilt, wenn auch in umgekehrtem Sinne, für Neger. Früher war man der Ansicht, dass Diabetes bei Negern nicht vorkommt. Später hat sich ergeben, dass dies falsch ist. Es dürfte keinerlei Unterschied vorliegen, wenn man das Material mit einem aus derselben sozialen Schicht von Weissen mit gleicher Altersverteilung vergleicht.

Experimentelle Diabetesforschung und Diät

Es besteht eine reiche Erfahrung darüber, dass eine Diät, die eine begrenzte Menge Kohlehydrate und eine erhöhte Menge Fett enthält auf Diabetes günstig wirkt. Der Blutzucker sinkt und die Symptome verschwinden bis zu einem gewissen Grade. Ähnliche Erfahrungen wurden im Tierversuch erhoben. Diese Untersuchungen sagen aber nicht so viel über das Problem, das uns interessiert, nämlich ob Fett auf längere Sicht schädlich wirkt. Der augenblickliche Effekt kann ja vorteilhaft sein, obwohl man im weiteren Verlauf eine ungünstige Wirkung erhält.

Die Untersuchungen, die zum Ziele hatten die Wirkung einer fetthaltigen Diät auf längere Sicht zu ermitteln, sind gering an der Zahl und in gewisser Hinsicht einander widersprechend. Die

Fettwirkung bei Alloxandiabetes wurde von BURNS, LEWIS und KELSEY sowie ABELIN studiert. Trotz verschiedener Versuchsanordnungen und Diätwahl kommt man in beiden Fällen zum Schluss, dass eine Erhöhung des Fettgehaltes unter der Voraussetzung günstig wirkt, dass man solche Fettarten anwendet, die der Verdauungskanal verträgt. Zum selben Ergebnis kommen auch JANES und PROSSER, während das von HOUSSAY und MARTINEZ in gewissem Masse verschieden ist. Letztere Autoren arbeiteten mit Ratten, bei denen der grösste Teil des Pankreas entfernt worden war. Es zeigte sich, dass die Tiere, die hauptsächlich mit Fett ernährt worden waren, alle innerhalb von 2 Monaten eingegangen waren. Die Tiere, welche hauptsächlich Kohlehydrate erhalten hatten, gingen in derselben Zeit in 78 % ein und die, welche hauptsächlich Protein erhalten hatten, in 56 %. Man hat diese Ergebnisse so erklärt, dass Fett besonders schädlich ist und die Gesundung verhindert. Diese Erklärung ist aber nicht die einzig vorstellbare. Aus den Werten kann auch darauf geschlossen werden, dass die Tiere, die zu viel Fett erhalten haben, wenig Eiweiss bekamen und dass der schädliche Faktor im Fehlen des Eiweisses zu suchen ist. In der Tat gehen die Mortalitätswerte mit der Eiweisszufuhr aber nicht mit der Fettzufuhr parallel. Ausserdem hat sich ergeben, dass Glutathion günstig für die Genesung wirkt. Bausteine für diese Substanz sind nicht im Fett vorhanden, können aber in Eiweiss vorkommen. Vielleicht ist Eiweiss gerade aus diesem Grunde besonders vorteilhaft. In diesem Zusammenhange soll erwähnt werden, dass WISSLER, FINDLEY und FRAZIER (1949) eine »Zwangsausfütterung» mit Glykose bei einer geringeren Anzahl von Ratten angewandt haben. Als diese dann nach etwas mehr als einem Monat getötet wurden, wiesen sie eine recht ausgeprägte Hyperplasie der Langerhansschen Inseln auf. Das Ergebnis ist ja nicht unerwartet. Die starke Hyperglykämie hat wahrscheinlich eine besonders kräftige Insulinproduktion erzwungen und deswegen sekundär zu einer Hypertrophie geführt. Im übrigen soll erwähnt werden, dass diese Ratten, wahrscheinlich vor allem auf Grund des hohen Blutzuckergehaltes, sehr fett geworden waren.

Fettleibigkeit und Diabetes aus theoretischen Gesichtspunkten

Es muss ein regulierender Mechanismus vorhanden sein, der sicherstellt, dass der Blutzucker nicht allzusehr vom Normalen abweicht. Sinkt er beträchtlich unter normale Werte (etwa 100 mg%), so bedingt dies Bewusstlosigkeit und bei langer Dauer Tod (Insulinvergiftung). Beginnt der Blutzucker zu sinken, müssen entweder Nahrungsstoffe aus den Depots des Körpers mobilisiert werden oder auch alimentär Nahrung zugeführt werden. Wir wissen, dass bei sehr geringer Insulinproduktion der Blutzuckerwert zunimmt. Dies deutet darauf hin, dass ein besonderes Zentrum oder die Gewebe im allgemeinen eine Tendenz haben, bezüglich der Stärke der Verbrennung zu reagieren.

Diese Überlegung führt also dazu anzunehmen, dass das evt. vorhandene Zentrum für die Regulation des Blutzuckergehaltes eigentlich nicht für den Blutzuckergehalt sondern für die Stärke der Verbrennung empfindlich ist. Eine weitere Stütze für diese Annahme ist, dass falls man bei niedriger Insulinproduktion fetthaltige Nahrung zuführt, der Blutzucker nicht so hoch sein muss. Ist dies nicht der Fall, so kommt es durch die geringe Insulinproduktion zu einer so starken Steigerung des Blutzuckers, dass die Nierenbarrière nicht funktionieren kann und Zucker im Urin ausgeschieden wird (bei einem Blutzuckerwert von etwa 150 mg%). Eine beträchtliche Erhöhung des Blutzuckerwertes während einer längeren Zeit kommt eigentlich nur bei Diabetes vor. Im übrigen soll hervorgehoben werden, dass die Zuckermenge, die normal im Blute vorhanden ist, ungefähr 5 g beträgt und dass eine Zunahme des Blutzuckers teils durch Zuckeraussonderung durch den Urin und teils durch Ablagerung von Zucker in Form von Glykogen wieder auf normale Werte zurückgeführt wird. Dieser Sicherheitsmechanismus, der gegen eine Blutzuckererhöhung vorhanden ist, funktioniert mit anderen Worten in einer Weise, dass er beim Diabetiker zu einem Zuckerverlust und Abmagerung führt, gleichzeitig besteht aber bei Diabetes ein Streben danach, den Blutzuckerwert hoch zu halten, wenn die

Diät nicht besonders fetthaltig ist. (Eine fettreiche Diät wirkt wie bekannt prophylaktisch gegen eine Blutzuckererhöhung.) Bei normaler Diät bedingt ein hoher Blutzuckergehalt teils, dass viel Zucker mobilisiert werden muss und teils, dass der Appetit zunimmt, so dass der Kranke hungrig ist und zu viel isst. Der erhöhte Appetit dürfte gemäss einer von mir aufgestellen Theorie (DAHLBERG 1949) dadurch bedingt werden, dass die erhöhte Mobilisierung von Nahrungsmitteln eine Absonderung von Stoffen aus den Geweben bedingt, welche das Appetitzentrum reizen. Vom Gesichtspunkt des Appetits ist es mit anderen Worten ein Unterschied ob der hohe Blutzuckergehalt auf zugeführter Nahrung beruht, wobei es zu keiner Erhöhung des Appetits kommt, sondern ein Sättigungsgefühl eintritt, oder ob die Erhöhung auf mobilisiertem Zucker beruht, wobei es zu gesteigertem Appetit kommt, je nachdem wie stark diese Mobilisierung ist.

Dieser Mechanismus erfordert also die Annahme von zwei Zentren: 1) ein Appetitzentrum, das in der Thalamusregion liegen soll und Verbindung mit dem sympathischen Nervensystem, vor allem mit den Nervenfasern, die zum Magen gehen, hat und 2) ein Zentrum für den Blutzucker, das vermutlich beim sog. Zuckerstich gereizt wird und in der Nähe des 4. Ventrikels liegen dürfte und Verbindung mit der Hypophyse und evt. den Nebennieren hat und mit deren Hilfe den Blutzucker reguliert.

Wir kommen auf das Problem Fettleibigkeit und Diabetes zurück. Wir haben gezeigt, dass für die Ansicht, dass Fettzufuhr schädlich sein soll oder, dass fettleibige Personen auf Grund ihrer Diät ein grösseres Risiko haben sollen an Diabetes zu erkranken als andere, keine Stütze vorhanden ist. Ein ursächlicher Zusammenhang folgender Art dürfte am nächsten liegen: Kommt es plötzlich zu einem starken Insulinmangel, so tritt ein Verlust an Zucker durch den Urin ein und es kommt zur Abmagerung. So verhält es sich besonders bei jungen Personen. Entwickelt sich der Insulinmangel hingegen langsam, so kommt es zu einem längeren Zwischenstadium, in welchem der Blutzucker erhöht ist, wobei die Erhöhung aber nicht den Grenzwert, welchen die Nieren für die Aussonderung von Zucker im Urin setzen, überschreitet. In diesem Stadium muss der hohe Blutzuckerwert eine Appetiterhöhung

bedingen ohne dass es gleichzeitig zu Verlusten durch den Urin kommt. Der erhöhte Appetit, dessen Ziel es ist, den hohen Blutzuckerwert aufrechtzuerhalten, bedingt eine vermehrte Ablagerung. In diesem Stadium werden die Patienten auf Grund des erhöhten Appetites dick. Dass fettleibige Personen relativ oft zuckerkrank werden, beruht also darauf, dass Fettleibigkeit ein Symptom für Diabetes sein kann, wobei sich dieser langsam ausbildet. Diese Diabetesform kommt im übrigen hauptsächlich bei älteren Personen vor. Es ist deswegen nicht wahrscheinlich, dass fettleibige Personen eine Disposition für Diabetes haben, sondern Personen mit Diabetesdisposition werden erst fettleibig, ehe die Symptome ernster werden und ehe sie im Urin Zucker ausscheiden und abmagern.

Zusammenfassend kann festgestellt werden:

1) Die zahlenmässigen Angaben, die über Diabetesfrequenz und Mortalität vorliegen, erlauben keinerlei Schlüsse darüber, dass erhöhter Fettverbrauch Diabetes hervorruft;

2) Die spärlichen experimentellen Untersuchungen auf diesem Gebiete erlauben ebenfalls keine solchen Schlüsse;

3) Aus theoretischen Gesichtspunkten liegt es am nächsten anzunehmen, dass Personen, deren Diabetes sich langsam ausbildet, unter der frühen Periode der Krankheit an Gewicht zunehmen und erst später Diabetessymptome bekommen. Aus diesem Gesichtspunkt kann man sich vorstellen, dass Personen, die im erwachsenen Alter ohne Veränderung ihrer Lebensart beginnen eine Gewichtserhöhung aufzuweisen, später Symptome für Diabetes bekommen werden.

Summary

Available figures concerning the incidence of diabetes and the

1) Available figures concerning the incidence of diabetes and the mortality in this disease do not give any idea as to whether diabetes might be caused by an increased consumption of fat.

2) Nor is it possible to draw any conclusion from scanty information obtained in experimental investigation.

3) From a theoretical point of view the most probable supposition is that patients in whom diabetes develops gradually gain

weight at an earlier stage of the disease, before the symptoms of diabetes have appeared. It is therefore possible that subjects who in adult life start to gain weight without any alterations in their mode of living will later develop symptoms of diabetes.

Résumé

1) La statistique sur la fréquence et la mortalité du diabète n'autorise nullement la conclusion selon laquelle une consommation accrue de matière grasse l'aurait pour cause.

2) Les rares expériences et recherches dans ce domaine ne permettent pas davantage de telles conclusions.

3) Du point de vue théorique on serait amené à supposer que les personnes affectées de cette maladie augmentent de poids et ne présentent les symptômes du diabète qu'à un stade ultérieur. De ce point de vue-là, on peut imaginer que les personnes qui commencent à l'âge adulte, sans changement de régime, à accuser une augmentation de poids, présenteront plus tard des symptômes du diabète.

Sumario

1) Los datos numéricos que se tienen sobre frecuencia de diabetes y mortalidad no permiten conclusiones de ninguna clase en lo referente a la cuestión de si un consumo aumentado de grasa produce diabetes.

2) Los escasos estudios experimentales dentro de esta esfera no permiten tampoco ninguna conclusión.

3) Desde el punto de vista teórico es lo más probable suponer que las personas que tienen esta enfermedad aumentan primero de peso y adquieren después los síntomas de la diabetes. Desde este punto de vista es posible comprender que las personas que en edad adulta sin ninguna alteración en su modo de vivir empiezan a mostrar un aumento de peso, tendrán posteriormente los síntomas de la diabetes.

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FROM THE SURGICAL DEPARTMENT OF KRONPRINSESSAN LOVISA'S CHILDREN'S HOSPITAL, STOCKHOLM.
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Duodenal Atresia and Stenosis

by

TH. EHRENPREIS and PH. SANDBLOM

In the field of intestinal obstruction in the newborn there is still much confusion regarding terminology.

Definition. Intestinal obstruction is called intrinsic or intramural when passage is impaired by changes in the intestinal wall itself and extrinsic or extramural when the obstruction is due to external compression. Intrinsic obstruction is either total or partial, these conditions being denoted, respectively, as atresia and stenosis. These several kinds of intestinal obstruction should be strictly separated, as there are definite differences in origin, symptoms, diagnosis, treatment, and prognosis.

Historical Notes. Prior to 1911 no case of atresia or pronounced stenosis of the digestive tract (anal atresia excluded) had survived. The first successful operation was performed by FOCKENS (1911) on a newborn baby with ileal atresia. A second survival was reported by LICHTENSTEIN (1916); the case concerned an infant seven weeks old with jejunal stenosis operated upon by ALEMAN in 1913. In 1916 ERNST reported on the first case of duodenal atresia cured by operation. LADD (1928) reported the first survival after surgical correction of congenital atresia of the bile ducts. The first successful operations for oesophageal atresia were performed in 1939 by LEVEN (1941) and — twenty four hours later — by LADD (1944).

These milestones in the development of malformation surgery have been followed by a steadily increasing number of reports of single successfully treated cases. Series of extrinsic intestinal obstruction in the newborn have been reported by MORTON &

JONES (1936) and by MCINTOSH & DONOVAN (1939). The only larger series of intestinal atresia and stenosis reported are from the Children's Hospital in Boston. A summary of a series of papers published by LADD and associates is given in Table 1; cases of extrinsic duodenal obstruction are included.

Table 1

Summary of reports on congenital obstructions of the digestive tract from the Children's Hospital in Boston.

Author	Year	Oesoph. Atr.		Intrins. Duod.		Extrins. Duod.		Total Intest. Intr.	
		Number	Recov.	Number	Recov.	Number	Recov.	Number	Recov.
LADD	1932	—	—	5	3	6	5	—	—
LADD	1936	—	—	—	—	—	—	53	10
LADD	1937	—	—	13	7	26	19	—	—
LADD & GROSS	1941	—	—	16	8	44	27	74	17
LADD	1944	34	11	—	—	—	—	—	—
SWENSON & LADD	1945	64	19	24	14	—	—	—	—
SWENSON	1947	20	16	—	—	—	—	—	—

As will be seen from this tabulation, the number of cases treated is steadily increasing, and the results, although still far from satisfactory, show a definite trend towards amelioration.

It was felt that our series of intestinal obstructions in the newborn from Kronprinsessan Lovisa's Children's Hospital should be reported in order to add to the information available in the few series reported hitherto. Our first three cases of intrinsic intestinal obstruction have already been described by PERMAN (1937). Later thirty six cases of intestinal obstruction in the newborn covering a ten year period were briefly reviewed in a paper read before the Swedish Society of Surgeons (EHRENPREIS 1943). Twenty three cases of duodenal obstruction in the newborn (intrinsic and extrinsic) were reported at a meeting of the Paediatric Society of South Sweden (EHRENPREIS 1945). Ten cases of megacolon in the newborn were analyzed by EHRENPREIS (1946).

Our first seven operations for oesophageal atresia were reported by SANDBLOM (1948).

The following constitutes a report on twenty cases of *duodenal atresia or stenosis* treated surgically during the last thirteen years. We have considered it preferable to discuss our series of intrinsic duodenal obstructions separately from cases of lower atresia and stenosis and also from extrinsic duodenal obstructions, the problems of diagnosis and treatment being rather different in these three groups.

Case Reports

Case 1. M. 641/36. Baby W., a full-term female infant, had bilious vomiting from birth. Only a scanty amount of meconium was passed and no stools followed. She was admitted at the age of four days. Except for a moderate dehydration physical examination showed nothing abnormal. On a flat x-ray the stomach and duodenum were seen to be greatly distended, no gas showing in the intestines beyond. The baby was operated upon twelve hours after admission (Pn). The diagnosis of duodenal atresia below the papilla of Vater was confirmed and a posterior gastrojejunostomy performed. Postoperatively the baby failed to improve and died two days after operation, having passed a normal stool the same day. At autopsy a membraneous atresia was found below the papilla of Vater. The anastomosis was patent and tight. There was a large haemorrhage into the peritoneal cavity.

Case 2. M. 723/36. In baby A.B., a full-term female infant, vomiting of bile-stained material started at the age of three days and increased continuously. Stools were scanty and contained some milk curds. The baby was admitted at the age of eleven days. Physical examination revealed slight dehydration and a certain prominence of the epigastrium. Conservative measures failed to relieve the symptoms. X-ray examination showed marked distension of the stomach and duodenum and only scanty gas bubbles in the intestines beyond. A small opaque meal was given; after one and a half hours only a small amount of barium had left the duodenum, outlining a marked narrowing of the intestinal lumen at the duodenojejunal junction. Operation performed at the age of twenty one days (Pn) confirmed the presence of a marked stenosis at the duodenojejunal junction. Posterior gastrojejunostomy was performed. The postoperative course was uneventful and the baby was dismissed three weeks after operation in excellent health. A follow-up examination at the age of four years revealed nothing abnormal in the development or state of the child.

Case 3. M. 169/38. Baby K.L. was a male infant, birth wt. 2 500 g. Vomiting started at the age of three days and soon became persistent. The vomitus was not bile-stained. Stools were of normal appearance but slightly diminished in number and size. On admission at the age of six days nothing abnormal was found upon physical examination. Under conservative treatment vomiting diminished and the baby thrived and gained rapidly. Vomiting, however, soon increased again, stools diminished, and there was a heavy loss of weight. As the condition of the child rapidly deteriorated operation became imperative. Laparotomy performed at the age of twenty four days (Hsh) revealed a marked narrowing of the duodenum above the papilla of Vater. Posterior gastrojejunostomy was performed. The child died two days after operation. At autopsy peritonitis was found, although no gross leakage from the anastomosis was evident. One and a half cm above the papilla of Vater there was a stenosis admitting a probe.

Case 4. S. 361/39. Baby L., a full-term female infant, had bile-stained vomiting from birth. A slight amount of meconium was passed but no faecal stools. She was admitted at the age of seven days. Physical examination revealed nothing abnormal. A flat x-ray showed marked distension of the stomach and duodenum with no gas present in the intestines beyond. Upon operation (Hsh) twenty four hours after admission atresia of the distal part of the duodenum was found. Antecolic duodenojejunostomy was performed. Postoperatively the child developed pneumonia, which proved fatal on the fifth day after operation. X-ray four days after operation showed moderate distension of the stomach, no duodenal distension, and a normal amount of gas present in the small intestine and large bowel. At autopsy the pneumonia diagnosis was confirmed. A membraneous atresia was present 1 cm below the papilla of Vater. The anastomosis was patent and competent and there was no peritonitis.

Case 5. M. 873/39. Baby L., a full-term female infant, had persistent vomiting of bile-stained material from birth. Small amounts of meconium and mucus were passed but no faecal stools. On admission at the age of six days the child was in very poor general condition, showing marked dehydration. Physical examination of the abdomen revealed nothing abnormal. Slight improvement resulted from conservative treatment. At the age of twelve days a flat x-ray was taken which showed marked distension of the stomach and duodenum but no gas beyond. Operation was performed at the age of fourteen days (Hsh). Atresia was found at or near the duodenojejunal junction and posterior gastrojejunostomy performed. The child expired eleven hours after operation. At autopsy a membraneous atresia was found below the papilla of Vater. There were no other abnormal findings.

Case 6. S. 933/39. In the case of baby G.S., a full-term female infant, there was vomiting of bilious material from birth. A small amount of slightly bile-stained mucus was passed. The baby was admitted at the age of three days. Physical examination revealed slight prominence of the epigastrium. On a flat x-ray the stomach and duodenum were seen to be greatly distended, no gas having passed beyond. At operation on the day after admission (Le) atresia was found at the duodenojejunal junction. Duodenojejunostomy was performed and a gastric tube left for decompression. The baby failed to improve and died twenty-four hours after operation. At autopsy a membraneous atresia was found at the duodenojejunal junction. Death had ensued through aspiration pneumonia. The anastomosis was patent and competent and there was no peritonitis.

Case 7. S. 1588/43. Baby R.M., a full-term male infant, began to vomit at the age of two days. Stools were scanty but otherwise normal. He was admitted at the age of four days. Physical examination revealed nothing abnormal. X-ray showed moderate distension of the stomach and duodenum. A small opaque meal was given. After one hour nothing had left the duodenum; after twenty four hours a small amount of barium had passed on to the large bowel, the larger part being still in the duodenum. Operation was performed at the age of seven days (Hsh). Stenosis was found at the duodenojejunal junction and posterior gastrojejunostomy was performed. The child died two days after operation. At autopsy peritonitis was found; there was no evidence of leakage from the anastomosis. A membraneous stenosis with an iris-like aperture the size of a match was present at the duodenojejunal junction.

Case 8. S. 1668/43. Baby H.S., a full-term male infant, vomited bile-stained material from birth on, sometimes more and sometimes less. Normal stools were passed daily. As vomiting increased and the baby began to lose weight, he was admitted at the age of one month. Physical examination revealed nothing abnormal. A small barium meal was given. After two hours only a small amount had left the duodenum, outlining a marked narrowing the size of a pin at the duodenojejunal junction. At operation (Hsh) four days after admission the stenosis diagnosis was confirmed and a duodenojejunostomy performed. The postoperative course was uneventful and the baby was discharged in perfect health seventeen days after operation.

Case 9. S. 598/44. Baby L.J. was male, birth wt. 2 630 g. Vomiting started at birth and increased in severity. Only small amounts of meconium were passed. At the age of three days the baby was admitted to the County Hospital of Falun. A barium meal was given and still had not left the dilated stomach and first portion of the duodenum after two hours. A diagnosis of duodenal atresia was made and the baby was

referred for operation to Kronprinsessan Lovisa's Children's Hospital. On admission at the age of five days he was feeble, with marked dehydration and loss of weight (2 030 g). The abdomen was not distended. X-ray examination showed that the barium meal given twenty-four hours previously was still in the stomach and first part of the duodenum. After correction of dehydration operation was performed at the age of seven days (Hsh). A cord-like atresia of the duodenum was found about five cm distal to the pylorus and a retrocolic duodenojejunostomy performed. After operation vomiting diminished and an increasing number and amount of normal stools with milk curds were passed from the second postoperative day. Five days after the operation wound disrupture occurred and vomiting again increased. The abdominal wound was resutured but the condition of the child steadily grew worse and he died on the fourteenth postoperative day. Autopsy showed a leak in the anastomosis with diffuse peritonitis.

Case 10. S. 774/44. Baby B.W., a full-term male infant, vomited bile-stained material from birth. A little meconium was passed but otherwise no stools. He was admitted at the age of seven days. Physical examination showed slight jaundice and moderate dehydration; the abdomen was not distended. X-ray examination revealed total obstruction of the second portion of the duodenum. The stomach and duodenum above the obstruction were markedly distended and there was no gas beyond. Operation was performed the same day (Es). The diagnosis of duodenal atresia was confirmed and a retrocolic duodenojejunostomy performed. Vomiting continued, however, and no stools were passed. The boy died on the seventh postoperative day. At autopsy a membraneous atresia was found at the same level as the papilla of Vater. There was a leak in the anastomosis with surrounding peritonitis.

Case 11. S. 1535/44. In baby T., a full-term male infant, vomiting of bilious material started at the age of three days and increased on the following days. A small amount of milk curds was noticed in the stools. At the age of four days he was admitted to the County Hospital of Falun. A barium meal showed total gastric retention after seven hours. The boy was referred for operation to Kronprinsessan Lovisa's Children's Hospital at the age of six days. Physical examination showed moderate dehydration and slight prominence of the epigastrium. Operation was performed the same day (Hsh) and confirmed the diagnosis of marked stenosis of the distal portion of the duodenum. A posterior gastrojejunostomy was performed. Seven days after operation wound disrupture and eventration occurred. The operative wound was resutured and the further course was uneventful. Gastrointestinal series three weeks after operation showed prompt passage of the opaque meal, in part through the anastomosis, in part through the stenosed duodenum. The baby was dismissed in perfect health one month after operation.

Case 12. M. 685/45. Baby M., a premature male infant with a birth wt. of 2 300 g, began to vomit bilious material soon after delivery. No meconium or stools were passed. Vomiting increased and on the third day he was admitted to the hospital. Physical examination gave normal results. A flat x-ray showed a total absence of gas in the intestines. There was a moderate amount of gas in the stomach and first portion of the duodenum but no dilatation of these parts. A small opaque meal passed readily into a moderately dilated duodenum, where it remained during the whole series (twenty four hours). Operation was performed at the age of three days (Es). Atresia of the distal portion of the duodenum was found. A duodenojejunostomy was performed followed by a gastrostomy with the object of obtaining more efficient decompression. During the next few days the gastrostomy output showed a steady decrease, the amount of stools increasing accordingly. On the seventh postoperative day disrupture of the operative wound occurred. Resuture was performed but the child failed to improve and died eight days after operation. Autopsy showed that the duodenum ended blindly at the duodenojejunal junction, having no connection with the proximal blind end of the jejunum. Circumscript peritonitis was found around the anastomosis but no gross leakage.

Case 13. S. 2194/45. Baby M.H., a female twin who weighed 2 300 g at birth, began to vomit bile-stained material when two days old. No meconium was passed. She was immediately admitted to the hospital. Physical examination showed slight dehydration and slight prominence of the epigastric region. On a flat x-ray plate the distended stomach and duodenum were in marked contrast to the gas-free intestines below. Operation was performed at the age of three days (Es). Atresia of the distal portion of the duodenum was found and antecolic gastrojejunostomy was performed around an indwelling gastric tube, the tip of which was left in the efferent jejunal loop for feeding. Convalescence was uneventful and the baby was discharged in perfect health one month after operation. At the age of nine and a half months she was still thriving, having developed quite normally, and weighed seven and a half kg. An opaque meal passed the anastomosis promptly, none of it passing through the duodenum.

Case 14. S. 2429/47. Baby J., a male infant, birth wt. 2 660 g, began to vomit a few hours after delivery. The vomitus was not bilious. Meconium was passed but no faecal stools. Physical examination on admission at the age of five days showed marked dehydration but otherwise nothing abnormal. A flat x-ray showed a small amount of gas in the stomach but no gas in the intestines. A small opaque meal was given. After twelve hours no barium had passed the pylorus. A barium enema showed the large bowel to be normally rotated. Duodenal obstruction through bands was considered to be the most likely explanation of

the findings. Upon operation at the age of six days (Es) rather unusual conditions were found. The pylorus was markedly thickened but not quite as firm and white as is usually the case in hypertrophic pyloric stenosis. The stomach was moderately distended and its wall slightly hypertrophied. The duodenum was also moderately dilated as far as to the duodenojejunal junction, the intestines beyond being uniformly collapsed, the size of an ordinary pencil. Water injected through the indwelling stomach tube readily passed the pylorus and the duodenum and entered the small intestines. A catheter inserted through a gastrostomy passed through the pylorus but stopped at the duodenojejunal junction. There was no extrinsic obstruction. A diagnosis of pyloric stenosis and duodenal stenosis was made and a posterior gastrojejunostomy performed. The indwelling stomachal tube was pulled through the anastomosis into the jejunum for feeding. On the following day the diagnosis of duodenal stenosis was confirmed by administration of a small barium meal which passed through the pylorus alongside the indwelling tube and filled the duodenum as far as the duodenojejunal junction, but did not pass beyond. Apart from a slight infection of the operative wound the postoperative course was uneventful. The baby was dismissed in perfect health six weeks after operation. A barium meal given at the age of two and a half months showed normal passage through the anastomosis.

Case 15. S. 921/47. Baby M.S., a full-term female infant, showed cyanosis immediately after normal delivery and was referred to the Medical Department of Kronprinsessan Lovisa's Children's Hospital. Vomiting of bile-stained material started the day after admission, increasing amounts being expelled during the next few days. Meconium was passed but no faecal stools. Physical examination gave essentially normal results. X-ray examination at the age of two days showed a large stomach and duodenum distended with gas, while the intestines beyond were free from gas. A small barium meal was given. After twelve hours no barium had left the duodenum. Operation at the age of three days (Sm) revealed a marked stenosis in the second portion of the duodenum. Retrocolic gastrojejunostomy was performed and the indwelling stomachal tube pulled through the anastomosis into the efferent jejunal loop for feeding. After operation the cyanosis gradually became more pronounced and the infant died four days later. At autopsy marked stenosis, barely admitting a probe, was found at the level of the papilla of Vater. The anastomosis was patent and its walls were tight. There was no peritonitis and no pneumonia. Examination of the skull revealed a tear in the tentorium with cerebral haemorrhage.

Case 16. S. 1409/48. Baby C.J.R., birth wt. 2 700 g, began to vomit darkish material soon after delivery. Small amounts of bile-stained stools were passed. As vomiting increased, the baby was admitted at the age

of five days. Physical examination revealed nothing abnormal except slight jaundice. A flat x-ray showed the stomach and first portion of the duodenum to be slightly distended and a small amount of gas to have passed into the intestines. A barium meal was given. After four hours no barium had passed. Operation was performed at the age of eight days (Sm). Marked stenosis was found in the second portion of the duodenum and an antecolic duodenojejunostomy performed. An attempt was made to pull the indwelling stomachal tube through the anastomosis into the efferent jejunal loop for feeding but the tip of the tube kept gliding back into the stomach. Postoperatively total gastric retention developed and showed no signs of decrease for four days. The condition of the child became critical. A second operation revealed that the duodenojejunostomy was patent and its walls tight. An enteroanastomosis was performed between the afferent and efferent jejunal loops and a tube was passed through a gastrostomy and the duodenojejunostomy into the efferent jejunal loop for feeding. After this second operation convalescence was uneventful and the baby was discharged in perfect health one month after admission.

Case 17. S. 1543/48. Baby L., a premature male infant weighing 1 910 g at birth, was referred to Kronprinsessan Lovisa's Children's Hospital for operation for anal atresia twenty four hours after birth. The infant had not been fed and had not vomited. Physical examination showed anal atresia; otherwise nothing abnormal was found. A flat x-ray in the inverted position showed a moderate amount of gas in the stomach and duodenum but no gas in the intestines beyond. A diagnosis of anal atresia and duodenal atresia was made and operation performed the same day (Es). Atresia of the first portion of the duodenum was found and a posterior duodenojejunostomy performed. The tip of the indwelling gastric tube was pulled through the anastomosis and left in the efferent jejunal loop for feeding. The condition of the infant during and after operation was satisfactory but nine hours later he suddenly died. At autopsy a membraneous atresia was found above the papilla of Vater. There was no peritonitis and no pneumonia. A small haemorrhage into the left cerebral ventricle was found; however, it seemed too small to account for the fatal outcome. It was felt that prematurity (weight at operation 1 670 g) in combination with operation was the main cause of death.

Case 18. S. 1758/48. Baby N., a premature male infant, weighed 1 950 g at birth. Vomiting started soon after delivery and increased during the first and second days of life. The material expelled was darkish and showed a positive reaction for blood, while tests for bile pigments were negative. A small amount of meconium was passed but no faecal stools. Physical examination at the age of two days showed

moderate dehydration and slight prominence of the epigastrium. A flat x-ray plate showed marked distension of the stomach and the first portion of the duodenum but no gas in the intestines beyond (Figs. 1—2). Operation was performed three hours after admission (Es) and showed an aplasia of the second and third portions of the duodenum. A posterior duodenojejunostomy was performed and attempts were made to introduce the tip of the indwelling gastric tube into the efferent jejunal loop. The tip kept gliding back into the stomach, however. A gastrostomy was performed and a tube was put through the anastomosis into the efferent jejunal loop for feeding. The postoperative course was uneventful. Jejunal feeding was maintained for thirteen days and the baby was dismissed in perfect condition twenty one days after operation.

Case 19. S. 2074/48. Baby L., a premature female infant, weighed 2 515 g at birth. Vomiting started after the first meal and increased successively in severity. Only small amounts of meconium were passed. At the age of five days a barium meal was given which showed moderate distension of the stomach and total gastric retention after four hours. There was no gas in the intestines. The child was transferred to Kronprinsessan Lovisa's Children's Hospital. Physical examination revealed marked dehydration but otherwise nothing abnormal. After correction of the dehydration and gastric lavage and suction, a flat x-ray showed small amounts of barium still present in the stomach twenty four hours after administration of the barium meal; no gas and no barium were visible in the intestines. Operation was performed at the age of six days (Es). A cord-like atresia of the first portion of the duodenum was found and a posterior gastrojejunostomy performed. The tip of the indwelling gastric tube was introduced into the efferent jejunal loop but kept gliding back into the stomach. A gastrostomy was added and a tube put through the anastomosis into the efferent jejunal loop and left for ten days for feeding. The postoperative course was uneventful and the baby was dismissed in perfect health three weeks after admission.

Case 20. S. 497/49. Baby F.H., a premature male infant, weighed 2 620 g at birth. Vomiting started soon after delivery and increased daily. Meconium was passed but no faecal stools. The child was admitted at the age of three days. Physical examination revealed moderate dehydration and jaundice. The abdomen was not distended. A flat x-ray showed a moderate distension of the stomach. Only small amounts of gas were present in the intestines. Operation was performed the same day (Em) and revealed a marked stenosis in the second portion of the duodenum. A posterior duodenojejunostomy was performed. The tip of the indwelling gastric tube was pulled through the anastomosis and left in the efferent jejunal loop for feeding. The postoperative course was uneventful. Jejunal feeding was maintained for nine days and the baby was discharged in excellent condition nineteen days after admission.

Incidence. The reports on the incidence of all kinds of congenital intestinal obstruction are most divergent. Out of 150 000 infants admitted to the Foundling Asylum of St. Petersburg, there were 9 cases of congenital intestinal obstruction (THEREMIN 1877); practically all the deceased were subjected to autopsy. The corresponding figures in Vienna were 2/111 451; autopsy was not uniformly performed. ERNST (1916) found 2 cases of atresia of the small intestines among 41 000 deliveries at the Royal Lying-in Hospital of Copenhagen. SHELDON (1926) reported 26 cases of intestinal atresia and stenosis out of 6 000 autopsies performed at the Hospital for Sick Children in Great Ormond Street in London since 1900. Our ten year series of intestinal obstruction in the newborn (EHRENPREIS 1943) numbered 36 cases, half of this series being intrinsic obstructions. During the same period 108 cases of intussusception were treated. Thus the proportion of intrinsic intestinal obstruction in the newborn to intussusception should be 1 : 6. Actually there is probably a somewhat higher proportion of congenital intestinal obstructions, as cases of atresia, especially of the duodenum, still not too infrequently die undiagnosed and thus are not included in our hospital series.

With regard to the relative incidence of the different sites of intrinsic obstruction there is more agreement, as appears from Table 2.

Table 2

Incidence of different sites of intrinsic obstruction.

Author	Year	Number	Duodenum	Jejunum	Ileum	Colon	Multiple
TANDLER	1900	94	33	55		6	—
FORSSNER	1906	231	79	119		22	11
DAVIS & POYNTER	1922	401	134	60	101	39	67
SHELDON	1926	26	8	13		5	—
VALLOIS ET AL.	1927	244	33%	53%		10%	—
LADD & GROSS	1941	71	16	8	44	3	3
EHRENPREIS	1943	18	11	0	4	1	2

In most of the reports duodenal obstruction accounted for about one third of the total of intrinsic obstructions, the series of LADD & GROSS and EHRENPREIS showing divergencies in opposite directions. In view of the shortness of the duodenum as compared with the intestinal tract as a whole, it is evident that obstruction in the duodenum occurs more frequently, relatively, than in any other part of the intestinal tract (TANDLER 1900, FORSSNER 1906).

A separate study of atresia and stenosis localization in series where separation is possible is tabulated below (Table 3).

Table 3

Incidence of different sites of atresia and stenosis separately.

Author	Year	Atresias						Stenoses				
		No.	Duod.	Jej.	Ileum	Colon	Mult.	No.	Duod.	Jej.	Ileum	Colon
TANDLER	1900	94	33	55		6	—	—	—	—	—	—
FORSSNER	1906	204	62	110		21	11	27	17	9		1
SHELDON	1926	22	6	13		3	—	4	2	0		2
LADD & GROSS	1941	52	5	6	36	2	3	22	11	2	8	1
EHRENPREIS	1943	14	7	0	4	1	2	4	4	0	0	0

It is evident from all reports that duodenal localization is much more frequent among stenoses than among atresias.

Embryology. The works of TANDLER (1900) and FORSSNER (1906) have made it appear probable that intrinsic intestinal obstruction is due to an arresting of development at the time when the bowel is changing from a solid cord to a hollow tube, and that this arresting takes place prior to the twelfth week of foetal life.

Pathology. Intestinal atresia may be found in three forms: as a membraneous veil, as a cord-like structure connecting the two blind ends of the bowel, or as a total lack of structure between the two blind ends, an aplasia. Correspondingly, intestinal stenosis is found in two forms: as a membraneous septum with an iris-like aperture, or as a more or less constricted hollow tube. The rela-

tive incidence of these various forms as studied by FORSSNER (1906) in 134 autopsy specimens collected from the literature is tabulated below (Table 4).

Table 4

Incidence of various forms of intrinsic obstruction (after FORSSNER).

	Atresias				Stenoses		
	Membr.	Cord	Aplasia	Total	Membr.	Cord	Total
Duodenum	9	11	13	33	8	5	13
Small Intest.	18	23	27	68	6	0	6
Large Bowel	7	1	5	13	1	0	1
Total	34	35	45	114	15	5	20

Thus in this series the three different forms of atresia show a fairly even distribution, whereas the membraneous form prevails among the stenoses.

The site of obstruction within the duodenum has more often been below than above the papilla of Vater, as shown by Table 5. In our present series this is still more pronounced (14 below, 5 above, 1 level).

Table 5

Incidence of different sites of obstruction within duodenum as related to the papilla of Vater.

Author	Year	Number	Above	Level	Below	Unclassified
CORDES	1901	57	22	8	19	8
DAVIS & POYNTER ..	1922	134	59	—	75	—
GARVIN	1928	113	34	19	44	16

Clinical Picture. The one symptom constantly present is vomiting, occurring mostly after feeding and not, as in oesophageal atresia, during feeding. In atresia cases vomiting usually develops on the first day of life (Table 6) and the same is in many cases true of marked stenosis. If stenosis is slight the onset

Fig. 1.

Fig. 2.

of vomiting may be deferred for one or several weeks. The amount and frequency of vomiting increases with the degree of obstruction and with the amount of feeding. The material expelled is usually bile-stained, since the obstruction is usually below the papilla of Vater.

The passage of meconium and stools in the newborn is often not adequately observed. Theoretically there should be no bilious meconium in atresias below the papilla of Vater. Normal or nearly normal looking meconium is, however, sometimes reported in these cases. The absence of cornified vernix caseosa cells in the meconium upon microscopy (FARBER's test, 1933) is presumptive evidence that an intestinal atresia exists. In severe cases of stenosis the same conditions as in atresias may be found. If the stenosis is less pronounced, normal meconium and even normal stools with milk curds may be passed.

The most striking feature of physical examination is the absence of abnormal abdominal findings. Abdominal distension is not to be expected in duodenal obstruction. Sometimes a prominence of the epigastrium, indicating marked gastric dilatation, is observed. Dehydration is always more marked than in the normal newborn and if left untreated soon reaches extreme degrees.

Fig. 3.

Roentgenologic Findings. In most cases of duodenal atresia the flat x-ray picture is pathognomonic. Anterior films with the child in a prone (Fig. 1) or head-up (Fig. 2) position show marked gaseous distension of the stomach and duodenum above the atresia and a total lack of gas in the intestines beyond. Dilatation of the stomach and the duodenum is often extreme but may in exceptional cases be less pronounced or even absent, as in our Case 12. In the presence of the typical x-ray plate the administration of an opaque meal should be omitted, as it is dangerous. LADD AND ASSOCIATES have pointed out repeatedly that malignant pneumonia may develop through aspiration.

In cases of marked stenosis the findings may be identical. If the stenosis is less pronounced, gastric and duodenal dilatation are slight or even lacking (Cases 14 and 16) and gas is seen in the intestines beyond the obstruction (Cases 2 and 16). A small opaque meal may then be given; usually it will show dilatation above the obstruction and a more or less marked retention of the barium meal. With luck the stenosed zone may be visualized, as in Fig. 3. MELLINS & MILMAN (1946) have proposed insufflation of air as an aid to diagnosis in cases with little

or no gaseous distension. We have no personal experience with this method but it seems worthy of further trial.

Diagnosis. Repeated vomiting in the newborn should suggest congenital intestinal obstruction regardless of the presence or absence of physical findings. The child should immediately be transferred to a hospital adequately equipped for the treatment of these emergencies. Diagnosis should be confirmed or excluded by roentgenologic examination.

Differential Diagnosis. Extrinsic duodenal obstruction may cause the same symptoms and signs as duodenal stenosis. Malrotation may be recognized by giving a barium enema, thus revealing the abnormal position of the large bowel. This differentiation, however, is of less importance, as both conditions call for immediate operation.

Pyloric stenosis rarely shows symptoms before the second or third week of life and thus should not be difficult to differentiate from duodenal atresia and stenosis. Cases of slight stenosis with late appearance of vomiting may be mistaken for pyloric stenosis. Roentgenography gives conclusive differentiating evidence. The conditions found in our Case 14 are exceptional and do not alter these statements.

In this case a pyloric stenosis was combined with a duodenal stenosis. It was not possible to determine the part played in symptomatology by each one of these conditions separately.

The clinical findings in intestinal obstruction beyond the duodenum are characterized chiefly by abdominal distension and there is no difficulty in separating these different sites of obstruction.

During the last few years we have observed two cases of hepatic degeneration in newborn babies with pronounced gastric retention, suggesting duodenal obstruction. The cause of the liver damage could not be established in either of these cases. As this source of error has not previously been mentioned the case reports will be given.

S. 1319/42. Baby T.E. was a full-term male infant. Vomiting started soon after delivery and rapidly increased in amount and frequency. Meconium was passed at birth; no faecal stools followed. The infant was admitted at the age of seven days. Physical examination showed pronounced jaundice and dehydration but no abdominal distension was found. A flat x-ray plate showed a small amount of gas in the stomach and in the large bowel. A small barium meal was given, revealing total gastric retention after twelve hours. Operation (Hsh) was performed at the age of eight days. No intestinal obstruction was found. The liver was unusually large and showed signs of fatty degeneration, the bile ducts being of normal appearance. The infant died twenty four hours after operation. Autopsy confirmed the operative findings. Microscopy of the liver showed extensive degenerative changes.

S. 1646/48. Baby S., a full-term male infant, was admitted at the age of five days with a history of persistent vomiting since birth. A small amount of meconium had been passed but no faecal stools. Physical examination showed moderate jaundice and dehydration; a marked microcephalus was also found. A flat x-ray plate showed normal distribution of abdominal gas. A small barium meal was given and revealed total gastric retention after seventeen hours. A diagnosis of duodenal stenosis was made. On account of the microcephalus present it was felt that operation should be avoided. The child died at the age of eight days, no stools having been passed. At autopsy no intestinal obstruction was found; the liver showed signs of extensive fatty degeneration.

Treatment. It should be borne in mind that intestinal obstruction in the newborn is an abdominal emergency, requiring diagnosis and treatment without undue delay. The results of treatment depend on prompt recognition and adequate surgical correction of the anomaly. The steps in diagnosis have been mentioned above. It may be added that physical and roentgenologic examination should be performed immediately on the child's admission.

Preoperative Care. Pre- and postoperative care are as important as the operative procedure. Their purpose is to establish the most favourable conditions for wound healing on the one hand and to prevent the ill effects of intestinal obstruction on the other. Preoperative measures are instituted simultaneously with diagnostic measures immediately on admission. They comprise correction of dehydration and insertion of an inlying gastric tube. Chemotherapeutics are instituted to prevent or treat

aspiration pneumonia. Atropine is added to diminish mucus secretion. Vitamin K is administered whenever the prothrombin index is low.

If the diagnosis is settled by a plain x-ray, operation should be performed as soon as the above-mentioned preoperative measures have been instituted, preferably within three—four hours after admission. Administration of a barium meal causes a delay of five—six hours to allow for gastroduodenal suction and lavage. Further delay is not only unnecessary but directly inadvisable.

Operative Technique. Local anaesthesia has proved satisfactory in our experience. Additional ether has been given only exceptionally and only for peritoneal closure. Oxygen is administered throughout the operation and attention paid to the conservation of body heat.

Three types of operative procedure have been successfully used for the relief of intrinsic duodenal obstruction. MORTON & JONES (1936) reported a case in which the obstruction was relieved by making a longitudinal incision over the point of obstruction, destroying the obstructing membrane with electrocautery, and suturing the incision transversely. This method seems to come closer to restoring normal conditions than any other type of operation. The disadvantages are the difficulty of approach and of determining the type of obstruction present (whether membraneous or cord-like), the procedure being applicable to cases of membraneous obstruction only. In our series it has not been tried.

The two other types of operative procedure aim at restoring passage by anastomosing the intestinal lumen above and below the obstruction. Gastrojejunostomy and duodenojejunostomy have both been used successfully. Duodenojejunostomy is theoretically the more satisfactory of these two methods but technically slightly more difficult to perform. Gastrojejunostomy, on the other hand, seems to expose the child to the risk of future gastrointestinal disturbances, as reported by WEBB & WANGENSTEEN (1931) and LADD (1937). The question of possible risk of gastrojejunal ulcer in the future has not yet been settled.

The technical difficulties in performing these anastomoses are

caused by the great disparity in the size of the loops to be anastomosed, and especially by the extremely small size of the efferent loop. Provided that instrumental equipment and suture material are adequate, these difficulties are not hard to overcome, however; they are definitely less than those met with in dealing with oesophageal atresia. The anastomosis should preferably be performed in two layers of single sutures with 00000 catgut on a small atraumatic needle. The type of operation performed in our cases is reported in Table 6. No ill effects from gastrojejunostomy were observed in the five cases surviving this type of operation. Our present policy is to perform duodenojejunostomy whenever this is feasible without difficulty. If difficulties arise, we do not hesitate to use gastrojejunostomy.

Up to the end of 1945 our results with these two types of operations were extremely discouraging. Scrutiny of our operative deaths at that time (Table 7) reveals two main groups. The early postoperative deaths (Cases 1 and 3—7 inclusive) were caused by direct complications connected with the anomaly or operation. The deaths occurring later on (Cases 9, 10, and 12) were considered to be due to disturbances of wound healing. It was felt that nutritional and fluid balance disorders were the main causes of this disturbance. Infants, and especially newborn infants, are extremely sensitive to inanition and dehydration. There seems to be a need of something more than we are able to give them through administration of parenteral fluids, transfusions, and amino acids, and this something seems to be included in breast milk. As there is always marked gastroduodenal retention in connection with gastrojejunostomy and duodenojejunostomy in the newborn, oral feedings should be kept very low during the first five—six postoperative days, which may be the most important time from the point of view of wound healing. These considerations resulted in the adoption of an additional operative measure from the end of 1945 on (from Case 13 onwards). The inlying stomachal tube is introduced into the efferent jejunal loop before closure of the anastomosis and left for postoperative feeding. The value of this procedure has been confirmed by gratifying results since its adoption. We were especially impressed

Table 6

Synopsis of case reports.

Case No.	Year	Birth Weight g	Type of Obstruction		Relat. to Pap. of Vater	Age at Onset Days	Age at Op. Days	Type of Operation	Result
1	1936	3500	Atresia	Membr.	Below	1	4	Anterior GJ	Death
2	1936	3770	Stenos.	Canal	Below	3	21	Anterior GJ	Recov.
3	1938	2500	Stenos.	?	Above	3	24	Posterior GJ	Death
4	1939	4300	Atresia	Membr.	Below	1	8	Anterior DJ	Death
5	1939	3000	Atresia	Membr.	Below	1	14	Posterior GJ	Death
6	1939	3700	Atresia	Membr.	Below	1	4	Posterior DJ	Death
7	1943	3680	Stenos.	Membr.	Below	2	7	Posterior GJ	Death
8	1943	3650	Stenos.	Canal	Below	1	35	Posterior DJ	Recov.
9	1944	2630	Atresia	Cord	Above	1	7	Posterior DJ	Death
10	1944	3310	Atresia	Membr.	Level	1	7	Posterior DJ	Death
11	1944	3500	Stenos.	?	Below	3	6	Posterior GJ	Recov.
12	1945	2300	Atresia	Aplasia	Below	1	3	DJ	Death
13	1945	2300	Atresia	?	Below	2	3	Ant. GJ + jejunal tube	Recov.
14	1947	2600	Stenos.	?	Below	1	6	Post. GJ + jejunal tube	Recov.
15	1947	3580	Stenos.	Canal	Below	2	3	Post. GJ + jejunal tube	Death
16	1948	2700	Stenos.	?	Below	1	8	Anterior DJ	
							12	EA + jejunal tube	Recov.
17	1948	1910	Atresia	Membr.	Above	–	2	Post. DJ + jejunal tube	Death
18	1948	1950	Atresia	Aplasia	Above	1	2	Post. DJ + jejunal tube	Recov.
19	1948	2515	Atresia	Cord	Above	1	6	Post. GJ + jejunal tube	Recov.
20	1949	2620	Stenos.	Membr.	Below	1	3	Post. DJ + jejunal tube	Recov.

Table 7

Causes of death.

Case No.	Postop. Survival Days	Autopsy Findings	Mechanism	Ultimate Cause
1	2	Intraabd. haemorrh.	Operative lesion of umbilical vessels.	Operation complication
3	2	Peritonitis	Probably soiling at operation; no leak.	Operation complication
4	5	Pneumonia	Aspiration	Anomaly and operation complication.
5	0	No cause	Inanition-operative shock.	Delayed diagnosis
6	1	Pneumonia	Aspiration	Anomaly and operation complication.
7	2	Peritonitis	Probably soiling at operation; no leak.	Operation complication
9	14	Peritonitis	Leakage from anastomosis.	Disturbance in wound healing.
10	7	Peritonitis	Leakage from anastomosis.	Disturbance in wound healing.
12	8	Peritonitis	Leakage from anastomosis.	Disturbance in wound healing.
15	4	Cerebral haemorrh.	Tentorial rupture	Birth injury
17	0	No cause	Prematurity-operative shock.	Prematurity

by the prompt amelioration in the postoperative course in Case 16 following introduction of the jejunal tube in the second operation. Further confirmation was provided when we started operating on cases of oesophageal atresia and were able to note the smooth postoperative course in these cases, nourished postoperatively in a similar manner. The value of a high-caloric and high amino-acid diet administered early postoperatively has been established by Co Tui et al. (1944) in a gastrectomy series fed by means of an Abbot-Rawson double tube (one stomachal for suction and one jejunal for feeding). A short time after we had adopted the use of a jejunal tube for feeding Hicken et al. (1946) reported

using the same procedure in connection with gastrojejunostomy for the relief of extrinsic duodenal obstruction in two newborn infants and one case of duodenal stenosis.

Postoperative Care. Since introduction of the transanastomotic jejunal tube for feeding, postoperative care has been much simplified. Adequate amounts of breast milk may be administered starting immediately after operation. Amino acid mixtures may be added if desirable. A small transfusion of plasma or whole blood is usually beneficial immediately after operation to prevent operative shock and is often repeated on the first postoperative day. No other fluids need be given parenterally as long as the tube is functioning. The child is placed in an oxygen tent with constant temperature, humidity, and oxygen concentration. If gastric retention should develop, a second small-sized gastric tube may be introduced for temporary or constant suction; the material thus obtained may be administered through the jejunal tube.

In Case 13 the tube stayed in place for eight days, after which it glided back into the stomach and was removed. In Cases 14 and 16 the same thing occurred on the third and fourth postoperative days, respectively; in Cases 18—20 jejunal feeding was maintained for thirteen days, ten days, and ten days, respectively. In Cases 15 and 17 the tube was still in place when the infants died. After removal of the tube the amount of feedings was temporarily decreased, parenteral fluids being added for the next few days. The administration of chemotherapeutics was discontinued as soon as normal peroral passage was established. The postoperative course was uneventful in all of the surviving cases.

Results of Treatment. A summary of the operative results in our whole series as compared to the series of LADD & GROSS (1941) is given in Table 8.

Both series reveal a marked difference in the mortality rate in atresia and stenosis, respectively. The results in the series of atresia and stenosis show no gross divergencies when studied separately. The difference apparent from a comparison of the totals is due mainly to the prevalence of atresias in the present series and of stenoses in the series of LADD & GROSS. There seems

Table 8

Results of treatment.

Type of Obstruction	Type of Operation	Present Series			Ladd & Gross 1941		
		No. Cases	Deaths	Recov.	No. Cases	Deaths	Recov.
Duodenal Atresia	Gastrojejunostomy	4	2	2	1	0	1
	Duodenojejunostomy	7	6	1	4	4	0
	Total	11	8	3	5	4	1
Duodenal Stenosis	Gastrojejunostomy	6	3	3	2	1	1
	Duodenojejunostomy	3	0	3	8	2	6
	Total	9	3	6	10	3	7
Total		20	11	9	15	7	8

to be no appreciable difference in the mortality rate after gastrojejunostomy and duodenojejunostomy, respectively.

A further analysis of the results as shown in Table 6 reveals very slight if any improvement during the years 1936—end of 1945, inclusive. Since that time prospects seem to have changed decidedly for the better. This impression becomes still stronger when one considers the causes of death before and after the end of 1945 (Table 7). It is evident from this tabulation that the only two deaths after 1945 were both due mainly to conditions beyond our control, as opposed to all of the deaths before 1945.

This marked improvement seems to be the result of two main factors, namely, 1) earlier diagnosis and treatment (cf. age at operation in cases of atresia before and after 1945, Table 6) and 2) more efficient pre- and postoperative treatment. In this treatment we consider the adoption of postoperative feeding through a transanastomotic jejunal tube to be the most important single factor.

A summary of results before and since the end of 1945 is given in Table 9.

Table 9

Results of treatment.

Type of Operation	Type of Obstruction	No. Cases	Deaths	Recov.
Gastrojejunostomy or duodenojejunostomy only. (1936—December 1945)	Atresia	7	7	0
	Stenosis	5	2	3
	Total	12	9	3
GJ or DJ with transanastomotic jejunal tube. (December 1945—1949)	Atresia	4	1	3
	Stenosis	4	1	3
	Total	8	2	6

Summary

Twenty cases of intrinsic duodenal obstruction in the newborn operated upon at Kronprinsessan Lovisa's Children's Hospital since 1936 are reported. A brief survey of the pertinent literature is given. Clinical and roentgenological findings, treatment, and results of treatment are discussed on the basis of the series presented. The importance of pre- and postoperative treatment and especially of maintenance of the fluid and nutritional balance is stressed. Postoperative feeding through an indwelling transanastomotic jejunal tube has proved a simple and efficient means of accomplishing this.

Résumé

Atrésie et Sténose du Duodénum

On fait rapport de 20 cas d'obstruction du duodénum intrinsèque chez le nouveau-né, opérés à l'hôpital d'enfants Kronprinsessan Lovisas depuis 1936. On donne un exposé sommaire des écrits s'y rapportant. On y débat les constatations cliniques et radiologiques, les traitements et résultats de traitements en regard des séries présentées. On y souligne l'importance du traitement pré-opératoire et post-opératoire, et spécialement du maintien de l'équilibre liquide-élément nutritif. L'alimentation post-opératoire par un tube jéjunal transanastomotique intérieur a établi un moyen simple et efficace de nutrition.

Zusammenfassung

Duodenale Atresia und Stenosis

20 Fälle innerer duodenaler Obstruktion bei neugeborenen Kindern, die im Kronprinzessin Lovisas Spital seit 1936 operiert wurden, werden dargestellt. Ein kurzer Überblick der Literatur wird gegeben. Auf Grund der vorliegenden Fälle werden klinische und röntgenologische Befunde, die Behandlung und die Ergebnisse der Behandlung diskutiert. Man hebt besonders die Wichtigkeit der vor- und nachoperativen Behandlung und die Aufrechterhaltung der Flüssigkeit und Nährungsbalanz hervor. Nach dem operativen Eingriff hat sich die Nahrungszufuhr durch eine im Jejunum gehaltene, transanastomotische Sonde als einfaches und wirksames Mittel zur Erreichung dieses Zweckes gezeigt.

Sumario

Atresia duodenal y estenosis

Se exponen 20 casos de obstrucción duodenal intrinsica en el recién nacido, operados en el hospital Kronprinsessan Lovisas a partir del año 1936. Se da un breve resumen de la litteratura al respecto. Los hallazgos clinicos y radiologicos, el tratamiento y sus resultados se discuten basados en las series presentadas. La importancia del tratamiento pre y postoperatorio, y especialmente la mantención del equilibrio nutritivo y de liquidos. La alimentación postoperatoria a travez de un tubo transanastomotico yeyunal, ha resultado un medio simple e eficiente para cumplir con esto ultimo.

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Refractory Rickets

by

GUNNAR ENGLESON

The general rule that rickets is prevented and quickly cured by Vitamin D is occasionally broken by the rather rare case of so-called Vitamin D-resistant rachitis, the cure of which requires large doses of Vitamin D over a long period.

Occasionally this type of rickets appears as a complication of diseases in different organs or systems of organs. For instance, such a type, called rachitis hepatica by GERSTENBERGER (2), occurs in hepatic cirrhosis (1). The poor effect of Vitamin D in connection with this disease has been ascribed to reduced liver function, though this aetiology is denied by other authors (3) on the ground that parenterally-administered Vitamin D seems to have had a good effect in some cases.

Further, there is little or no response to treatment with Vitamin D in renal rickets and that form of rickets which develops with the syndrome of cystine diathesis described by FANCONI. Intestinal infections and disturbances of other kinds may also contribute at times to the delayed healing of rickets, thereby giving the temporary impression that the latter is resistant to therapy.

As a rule, however, we mean by Vitamin D-resistant rickets the rather uncommon form in which none of the aforementioned causes can be demonstrated. Thus it may be described as primary vitamin-resistant rickets (LÜSSY, 4).

A characteristic feature of this type is that it develops in spite of ordinary rachitic prophylaxis and that in ordinary doses Vitamin D is without effect. The serum concentration of the vitamin is stated to be normal. A pronounced hypophosphataemia belongs to the picture. The majority of the cases described in

the literature have reference to older children with a long history of rickets. There are cases, however, of vitamin-resistant rickets with a normal phosphorus level in the blood (7, 16). The author will return to this point later on.

Opinions vary concerning the causes of primary Vitamin D-resistant rickets. BORNSCHEUER (5) assigns great importance to a disturbance of the acid-base balance in the direction of acidosis, and therefore he recommends among other things a base-rich diet. Other workers (e.g. KÜSTER, 6) have not found this form of therapy to lead to any positive result, however. Among the theories which have been advanced as possible aetiological explanations are deficient »utilization» at the site of bone growth (GILL, 7) or a more general inability of the body to avail itself of Vitamin D (HIGHMAN and HAMILTON, 8); defective breakdown of Vitamin D into biologically active substances (BAKWIN, BODANSKY, and SCHORR, 9); too low a content of biologically active intermediate products of Vitamin D in the synthetic preparations (BEÜMER, 10); and familial susceptibility.

ALBRIGHT, BUTLER, and BLOOMBERG (11, 12, 13), who have made very extensive investigations into the calcium and phosphorus metabolism in various morbid conditions, consider that the cause of the poor effect exercised by Vitamin D is to be sought in an intrinsic factor. Further, the same authors are of the opinion that in vitamin-resistant rickets there is a secondary hyperparathyroidism, a view that is now rather widely accepted. Among other grounds they base this theory on anatomical findings (hyperplasia of the parathyroids) as well as metabolic ones (calcium and phosphorus balance tests). In this way the pronounced hypophosphataemia receives a ready explanation. Hypercalcaemia, which is also one of the symptoms of hyperfunction of the parathyroid glands, usually does not occur, however.

The treatment in the cases first described was entirely without result. However, thanks to the introduction of large daily doses of Vitamin D by ALBRIGHT and his co-workers, the prognosis has now become substantially better. With massive doses of the vitamin ranging from 150 000 to 1 million I.U. daily it has been

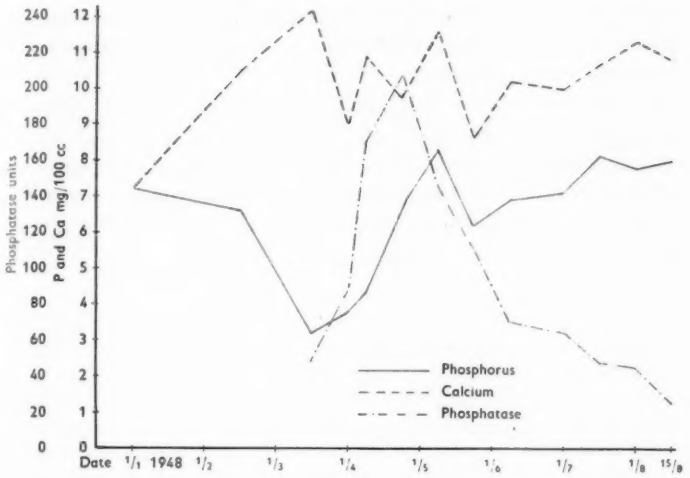

Fig. 1.

possible to obtain good results without demonstrable toxic secondary effects in the majority of the cases later described. Robinson and W. Nelson (14) have interpreted this effect on the basis of phosphorus, inulin, and diodrast clearance tests as due inter alia to the reduction by large doses of Vitamin D of the glomerular filtration of phosphorus.

Parathormone has been given to a number of these patients but has proved to be completely ineffective. As is known, while having no effect on the calcium absorption this hormone gives a powerfully increased excretion of phosphorus in the urine. Hence an anti-rachitic effect was hardly to be expected.

A.T. 10 has been tried by Albright and co-workers; Bakwin, Bodansky, and Schorr; Lüssy; and others with a negative result which is ascribed by the first-mentioned authors to the fact that A.T. 10 raises the urinary excretion of phosphorus and brings about a negative phosphorus balance. However, Bessau and Löhr (15) have reported two cases of vitamin-resistant rickets in which combined treatment with Vitamin D and A.T. 10 resulted in recovery, whereas Vitamin D alone did not. These authors have

accordingly employed a form of therapy for which the common indication is hypoparathyroid function. In both cases hypophosphataemia was registered.

A study of earlier published cases of Vitamin D-resistant rickets brings to light now and again cases which present somewhat deviating pictures. Therefore it has seemed justifiable to endeavour to shed some light on these problems in connection with a case of vitamin-resistant rickets treated in Lund which differed in some respects from »normal» cases of this type.

Case Report.

Boy, born Jan. 26, 1946. Next youngest of seven healthy brothers and sisters, in all of whom the past history was free from rickets. Birth wt. 2 900 grams. Breast-fed for eight months. Given the customary prophylactic dose of fish liver oil, about 1 500 I.U. daily. Sat up at nine months of age but could not stand with support until eighteen months of age; never able to walk. — When he was eight months old a mild rickets in the form of moderate epiphyseal enlargements was observed. On Dec. 29, 1947 — the patient was then one yr. eleven mo. old. — he was remitted to the Paediatric Department in Lund for bronchopneumonia and rickets. The bronchopneumonia receded under treatment with penicillin and sulfonamide preparations. During the first period of his subsequent stay in the hospital the patient had repeated throat infections as well as chicken-pox followed by an asymptomatic encephalitis.

On his admission pronounced rachitic skeletal changes were found, with powerful swellings of the epiphyses at wrists and ankles (typical so-called »double joints»). He had Harrison's groove and rickety rosary. No craniotabes. Distinct genua vara. He could not support himself on his legs. Fontanelle open one and one half finger-breadths, had soft edges. Dentition was delayed; he had in all twelve teeth, six in each jaw. His incisors, especially the inferior maxillary, were loose. A marked muscular hypotonia was present. Wt. 9 030 g, ht. 78 cm. No facial or peroneal signs. X-ray examination on Dec. 29, 1947, of cranium, spinal column, skeletal systems of thorax and upper extremities, including claviculae and scapulae, pelvic girdle, and bony system of lower extremities disclosed very greatly reduced calcium content. Fractures with callus formation were seen at several points within the ribs on both sides, in the claviculae and right fibula, and at the proximal ends of the right radius and ulna. All the metaphyses were rather much increased in breadth and greatly frayed. Further, lamellar periostal deposits were observed at several points along the long tubular bones (Dr. O. Olsson).

The laboratory findings are visualized on Curve 1. Serum calcium was determined by the KRAMER—TISDALL technique, serum phosphorus

by that of IVERSEN—ODIN, and the phosphatases by that of BUSH and BUSH (normal levels in children: max. 24 U.). On the patient's admission the calcium and phosphorus in the serum were at the same level, *viz.* 7.2 mg per 100 cc. During treatment with Vitamin D the phosphorus fell, reaching its lowest value after fully two and one half months' treatment. During the months following there was also a mild hypophosphataemia, but the level rose again and during the last four months it was normal to hypernormal. The calcium level also went up little by little and reached its maximum (12.2 mg per 100 cc.) when the serum phosphorus was at its lowest point. After this the blood calcium varied within approximately normal limits. Unfortunately the first phosphatase determination was not made until March 15, 1948. The value was then pathologically raised (50 U.). During the next month it gradually rose to a maximum of 208 U. Samples taken later showed successively falling values. On the patient's discharge from the hospital on Aug. 12, 1948, the level was 25 U.

Other Laboratory Tests. Titration of organic acids in the urine disclosed a pathologically elevated value on one occasion (about 40 cc N/10 HCl per 24 hrs. and kg body weight), but later tests showed normal values. Glucose tolerance reaction normal. Other liver-function tests (galactose tolerance, Takata Ara, bilirubin in serum, urobilin, urobilinogen in urine) also normal. N.P.N. normal the whole time. Heller's, Almén's, and other urine tests (sp.gr. and sediment) negative on repeated samples. No cystine in urine. Normal urogram. Normal excretion of 17-ketosteroids. Examination of faeces also gave normal results. Tuberculin negative. Wassermann negative. Initially there was a mild anaemia, then normal blood values. Repeated cardiograms always gave a normal result. No signs of Vitamin D poisoning in electrocardiogram.

The patient was initially treated with ordinary therapeutic doses of Vitamin D, *i.e.* 5—10 000 I.U. daily, the dose soon being raised to 15 000 I.U. In spite of this no healing tendency could be radiologically detected after fully six weeks' treatment. Not until after another month's treatment, during which period the patient was also administered a one-time massive dose of 500 000 I.U. of D_2 intramuscularly, could any signs be found on the radiograms of an increased calcification in the skeleton. Subsequently the Vitamin D doses were increased to 30 000 I.U. daily and the patient was given repeated injections of Vitamin D_2. After three and one half months' treatment, during which the patient received in all about $2\,^1/_2$ million I.U. of Vitamin D, partly by mouth and partly by injection, and additional quotas in the form of irradiation with a quartz-light lamp, the x-ray showed a palpably increased calcium content in the skeleton and in addition signs of good periostal deposition. X-ray films taken later showed a further increase in the calcium content of the whole skeleton and soon incipient normalization of the epiphyseal

lines. However, on the patient's discharge on Aug. 12, 1948, by which date he had received in all over 11 million I.U. of Vitamin D, a radiologically demonstrable healing of his rickets had not yet taken place. Besides this causal treatment, recourse was had to symptomatic. It was seen that he had a sufficient quantity of calcium and phosphorus in his food. A.T. 10 and parathormone were not tried.

The course of the disease was characterized by a slow improvement, and upon the patient's discharge after almost eight months in the hospital his rickets was well on the way toward recovery both clinico-radiologically and biochemically. His weight had increased about 1.7 kg. The skeleton had become hard. His fontanelle had closed after only a few months, and he had been able to walk for some time. He had almost all his teeth. His mental development was normal for his age. His bandy-legged condition remained but had diminished. Orthopaedic correction was not considered for the present. His height had not increased and thus there remained a rachitic dwarfism. No signs of Vitamin D overdosage were detected by the control methods employed for this purpose, *viz.* electrocardiogram, serum calcium, urine calcium by Sulkowitch's test, urine sediment, and renal x-ray examination (abdominal overhaul and urography).

Because of the progressive normalization of the blood chemistry, the x-ray findings, and his good general condition, the patient was discharged in the middle of August, 1948. Follow-up examinations in the Outpatient Department have hitherto shown *status quo.*

To summarize, this case has reference to a two year old boy who, in spite of routine rachitic prophylaxis with Vitamin D, developed a florid rickets which showed signs of being cured only after large doses of Vitamin D had been administered over a long period. The blood-chemical changes offered certain peculiarities that will be discussed below.

Discussion

A comparison between this patient's case of Vitamin D-resistant rickets and the majority of the cases described earlier will immediately reveal a number of differences. In the present case the course is distinctly more benign. The rachitic changes are healing in response to considerably smaller doses of Vitamin D than are generally required. Compared with the usual cases of this type, the blood-chemical changes are also quite different. Contrary to

the common finding, there was hyperphosphataemia (P/serum = 7.2 mg per 100 cc) when the patient was admitted to the hospital. After Vitamin D treatment for about two and one half months hypophosphataemia appeared, though this never reached the extremely low values that usually characterize these cases.

On admission the patient had hypocalcaemia, but was without signs of either latent or manifest spasmophilia. The serum calcium values rose later and subsequently varied within, on the whole, normal limits.

The phosphatase content of the serum was unfortunately not determined at the beginning. The first test was made when the serum phosphorus was at its lowest point and gave a distinctly pathologically raised level (50 U.). The phosphatases then increased successively to a maximum of 208 units, slowly declining later until the values were practically normal.

So far as the author knows there has been no case marked initially by a hyperphosphataemia among previously described »non-typical» cases of Vitamin D-resistant rickets, but GILL (7) has mentioned two cases and NADRAI (16) one where there were normal phosphorus values in the blood. Both of Gill's patients exhibited a striking resistance even to powerful treatment, though he obtained a fall of the phosphatases after several years' treatment and in one case also a mild tendency to radiological healing. There is no close agreement with the patient here reported. In the case described by NADRAI, in which Vitamin D by mouth and in the form of solar irradiation was without effect, a single massive dose of 25 mg of Vitamin D_3 intramuscularly led to complete recovery. This patient had severe intestinal disturbances at one and a half years of age. Her rickets dated from about this time (at the time of the examination she was four and a half years old), which fact obviously makes the case more difficult to judge. The origin of the rickets may to some extent be assigned to deficient intestinal reabsorption of Vitamin D. The therapeutic effect of parenterally-administered Vitamin D also points in this direction. In other words, this case cannot be classified definitely as primarily vitamin-resistant. It is a peculiar point that in an otherwise florid rickets a normal serum phosphorus value was

found. This patient too, however, presents a picture different from that of the author's case.

The cases reported by BESSAU and LÖHR, which responded to a combined treatment of Vitamin D and A.T. 10, also deserve some mention. Both of them concerned children aged two—three years with florid rickets. BESSAU and LÖHR themselves consider that the favourable result of the therapy was due among other things to the increased calcium reabsorption through A.T. 10. In spite of its close chemical relationship to Vitamin D, A.T. 10 generally has no anti-rachitic effect. This is considered by ALBRIGHT and his co-workers to depend in part upon the A.T.10's establishing a negative phosphorus balance. Further, A.T. 10 gives no constant increase in the serum phosphorus (SIWE, 17). It therefore seems strange that in these two cases such good results were obtained from A.T. 10 and Vitamin D. In animal experiments SIWE (17) has shown that the ultrafilterable fraction of serum phosphorus sometimes rises after administration of A.T. 10. Whether the effect attained in these two cases was also to some extent dependent on this circumstance cannot be decided with any certainty. The low serum phosphorus in them argues against a hypofunction of the parathyroids, the presence of which might otherwise have suggested itself on the basis of the therapeutic result.

Hence among cases of primary Vitamin D-resistant rickets patients are occasionally found who exhibit certain deviations that are to some extent incompatible and rather difficult to explain. The case reported here is another instance of this kind. What is the aetiology of these unusual findings? (The first thought which suggests itself, *viz.* that there have been laboratory errors, may be completely rejected. As always, double determinations were made; moreover the calcium and phosphorus determinations were carried out by a staff specially trained in this field. Further, the two first serum phosphorus measurements — with an interval of fully five weeks — both showed hypernormal values.)

The explanation might conceivably be as follows. For a period of about one year the patient was developing rickets and consequently failed to utilize the Vitamin D administered during

this time. This involved an increased load on the parathyroid glands, which had to answer almost alone for the calcium-phosphorus regulation. Ultimately, the parathyroids gave way and a certain amount of hypofunction arose leading to a diminished excretion of phosphorus through the kidneys and hence hyperphosphataemia. When Vitamin D was supplied in increased quantities later on, more calcium was reabsorbed from the intestinal canal. Bone formation also required phosphorus, which was taken from the blood with the result that the serum phosphorus level dropped. When the rickets began to heal, the phosphorus values rose again, though now as a sign of the healing process. While the treatment was going on the parathyroids had an opportunity to »take a rest», after which the excretion of parathormone gradually became normalized.

That symptoms of tetany did not occur initially despite hypocalcaemia may be accounted for on the ground that the cells of the body gradually adjusted themselves to a low calcium level in the serum. Analogous conditions are well known from the postoperative parathyreoprival tetanies, which may sometimes have hypocalcaemia without manifest symptoms of tetany. It is not solely hypocalcaemia as such, but the abrupt falls in the serum calcium which lead to the appearance of tetany symptoms (SIWE, 18). The low level shown by the serum calcium on the patient's admission may also be readily explained by the hypofunction of the parathyroids assumed above.

While the anti-rachitic treatment was being carried out the phosphatases showed a rise, which is not the rule. To account for this is difficult. Increased secretion of parathyroid hormone may probably be excluded. The highest values were recorded at a point when there was reason to assume that more calcium and phosphorus were available for new formation of bone. It appears reasonable to interpret the phosphatase increase as a sign of powerful ossification with a considerably raised osteoblastic activity. The decline in the phosphatases that took place later is in harmony with the other signs of healing. That the normalization proceeded slower than it did for the serum phosphorus is also according to rule.

Thus if the line of thought advanced here is correct, this patient with rickets refractory to Vitamin D probably had a transitory hypofunction of the parathyroids secondary to his rickets. This hypothesis is opposed to current opinion — hyperparathyroidism, but on the other hand, as pointed out above, other cases have been described which have deviated from the normal course; besides those previously cited, there is one (LINDER and VADAS, 19) in which hyperplasia was found anatomically on extirpation of one of the parathyroid glands but in which no obvious change either in x-ray findings or blood chemistry followed the operation, as well as another case without postmortem signs of parathyroid hyperplasia (LÜSSY, 4). In other words, a hyperfunction as well as a hypofunction of the parathyroids may be secondarily associated with Vitamin D-resistant rickets. The author would like to stress, however, that the views advanced here are quite naturally merely hypothetical. Still, the unique character of the case reported does not admit of its being placed in earlier known groups. The divergent blood-chemical changes and the benign clinical course shown by this patient are — so far as the author can see — best illuminated by and most comprehensible on the basis of the above-mentioned assumptions.

The primary cause of Vitamin D-resistant rickets has not admitted of being solved in any way by this case either. Whatever this cause may be, it is manifest that secondarily the parathyroids play an extremely important part in the clinical picture. Experience argues to some extent in favour of the involvement of other endocrine organs also. LÜSSY mentions, for instance, a case of Vitamin D-resistant rickets with pluriglandular insufficiency in which, at autopsy, a hypoplasia was found in several endocrine organs, perhaps most pronounced in the suprarenals. To be sure, in the case described here there took place a slow normalization and healing in most respects except height. Whether the cause of the patient's failure to increase in height is to be sought in a possible derangement of other endocrine organs is a question that quite naturally evades any reliable decision.

It is accordingly evident that cases of primary Vitamin D-resistant rickets may exhibit varying clinical pictures. This fact

suggests that the primary cause of the disease is uniform but that other organs — especially the parathyroids — are secondarily involved.

Summary

The author reports a case of Vitamin D-refractory rickets in a two year old boy which showed a good healing tendency from a clinico-radiological as well as a laboratory point of view after about eight months' treatment with altogether over 11 million I.U. of Vitamin D, administered partly by mouth, partly by injections, and partly in the form of light treatment.

On the patient's admission and for fully five weeks thereafter there was a hyperphosphataemia. A number of »non-typical» cases described earlier are discussed.

Résumé

Rachitisme refractaire

L'auteur relate un cas de rachitisme résistant aux vitamines D chez un garçon de 2 ans, qui, après un traitement de 8 mois d'en tout 11 millions U.I. de vitamines D — en partie par la bouche, en partie par injections, et en partie par un traitement lumineux — montra une tendance à une bonne guérison, tant du point de vue clinico-radiologique que du point de vue laboratoire.

A l'admission du patient, et durant les cinq semaines suivantes, il y avait hyperphosphatémie. On discute un certain nombre de cas »non typiques» précédemment cités.

Zusammenfassung

Refraktäre Rachitis

Der Verfasser erstattet einen Bericht über eine Vitamin D refraktäre Rachitis bei einem zweijährigen Knaben, welcher nach einer achtmonatigen Behandlung mit insgesamt über 11 Millionen I.U. Vitamin D — teilweise per os, teilweise durch Injektionen und teilweise in Form einer Lichtbehandlung — sich, sowohl vom klinischen als auch vom röntgenologischen Standpunkt betrachtet, auf dem Wege der Verbesserung befand.

Bei der Einlieferung des Patienten und volle fünf Wochen hindurch konnte man Hyperphosphatämie konstatieren. Es werden auch eine Anzahl früher gemeldeter, »nicht-typischer», Fälle diskutiert.

Sumario

Raquitismo refractario

El autor relata sobre un caso de raquitismo refractario a la vitamina D en un niño de dos años de edad, que despues de un tratamiento de aproximadamente 8 meses con administración de vitamina D 11-millones U.I. de vitamina D, parcialmente por boca y por via parenteral y en forma de irradiación solar, presento una tendencia a la curación tanto desde el punto de vista clinico-radiologico, como desde el punto de vista humoral.

El paciente tenia en el momento del ingreso y durante cinco semanas consecutivas una hiperfosfatemia. Se discute sobre casos atipicos descritos anteriormente.

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Überempfindlichkeitsreaktionen auf Quecksilber (Die Calomelkrankheit und die Akrodynie)

von

Prof. G. FANCONI

Seit vielen Jahren ist es uns aufgefallen, dass das Quecksilber auch in therapeutischen Dosen, intern oder als Salbe angewendet, häufig, besonders im Kleinkindesalter, allergische Reaktionen auslöst. Beim älteren Kind und beim Erwachsenen sind diese Quecksilberkrankheiten viel seltener und wir haben Gründe anzunehmen, dass sich bei vielen eine Art Immunität gegen das Hg als Allergen ausbildet, etwa wie bei der Nirvanolkrankheit. Übrigens kennen wir noch andere allergische Krankheiten, die aus irgend einem Grund auf das Kleinkindesalter beschränkt bleiben, so das Säuglingsekzem, manche Formen der Bronchitis asthmatica usw. Es bleibe dahingestellt, ob dabei Immunisierungsvorgänge oder altersbedingte Änderungen des Terrains vorliegen.

Die Frühreaktionen auf das Hg weichen je nach der Applikationsstelle etwas voneinander ab. So erzeugen die Salben vorwiegend lokale oder allgemeine Dermatitiden. Vom Darme aus entstehen hauptsächlich erythematöse Exantheme. Dagegen ist das klinische Bild der Spätreaktionen, z. B. die Akrodynie dasselbe, ob das Hg extern oder intern appliziert wurde.

Die Frühreaktionen stellen sich am 9. bis 10. Tag, die Spätreaktionen einen bis mehrere Monate nach dem Beginn der Behandlung ein. Bei mit Hg vorbehandelten Kindern kann es ähnlich wie bei der Serumkrankheit zu einer Sofortreaktion kommen, d. h. die Hg-Krankheit tritt innerhalb der ersten 24 Stunden nach Beginn der Behandlung ein.

Frühreaktionen. Die häufigste und neben den lokalen Dermatitiden nach Salbenapplikation die wichtigste ist die akute exan-

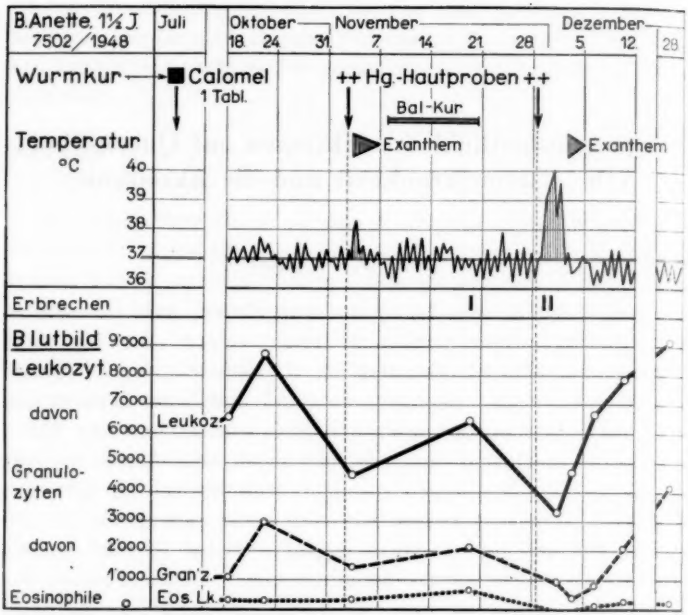

Abb. 1. Verlauf von Fall 2.

thematische Quecksilberkrankheit. Wir haben sie »*Calomelkrankheit*» genannt, weil in der Schweiz gerade das Calomel sehr häufig besonders als Bestandteil von »Wurmschokoladen» auch ohne Rezept in den Apotheken abgegeben wird. Die Calomelkrankheit haben wir jedoch auch nach protrahierter Salbenbehandlung, etwa beim Ekzem, Impetigo usw. gesehen, ja sogar bei einem mit Calomel vorbehandelten Kind schon nach einer Bloch'schen Läppchenprobe mit einer geringen Menge Hg-haltiger Salbe (siehe Fall 2).

Die Calomelkrankheit beginnt 5 bis 13, am häufigsten 8 bis 10 Tage nach Beginn der Quecksilbermedikation mit *Fieber* und allgemeinem Unwohlsein. Bald stellt sich ein generalisiertes, sehr wechselndes, polymorphes, zuerst scarlatiniformes, nach wenigen Stunden schon grossfleckiges morbilliform-urtikarielles *Exan-*

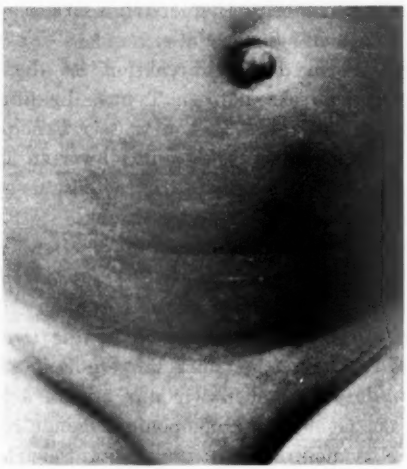

Abb. 2. Positive Kutanreaktion mit 2 % weisser Praecipitatsalbe vom 29.11. 48.

them ein. Zuerst wird die Fehldiagnose Scharlach, dann Masern, und schliesslich, wenn die Flecken noch grösser geworden sind, Megaloerythem gestellt. Wir vermuten sogar, dass manche, vielleicht sogar die meisten sogenannten Megaloerytheme nichts anderes als verkannte Calomelkrankheiten sind. Jedenfalls haben sich sämtliche Fälle der letzten Jahre, die mit der Diagnose Megaloerythem ins Kinderspital eingeliefert wurden, als Calomelkrankheiten entpuppt. Auch bei den sogenannten Masernzweiterkrankungen dürfte es sich häufig das eine Mal um Calomelkrankheit handeln. Neben dem Exanthem besteht eine generalisierte *Drüsen-*, häufig auch eine *Milzschwellung*. Im Blute sind die Leukozyten normal oder vermindert, im Gegensatz zu den Masern sind die *Eosinophilen* vorhanden oder gar vermehrt. Häufig ist die Diazo-Reaktion positiv. Katarrhalische Symptome der oberen Luftwege fehlen, *Conjunktivitis* kommt dagegen vor. Die Krankheit klingt innert wenigen Tagen ab.

Als Beweis für die Hg-Überempfindlichkeit fallen die *Cutanproben mit Hg-Salben oder mit Calomel* positiv aus (siehe Abb. 2),

und zwar bei allen Kindern in den ersten 4 Krankheitstagen, nach 6 Wochen nur noch in $^1/_4$ der Fälle.

Eine zweite Form der Frühreaktion ist die *generalisierte akute Dermatitis* vom ekzematösen Typus, die nur nach perkutaner Applikation von Hg, z. B. von weisser Präcipitatsalbe usw. auftritt. Sie kann sehr hartnäckig und schwer zu behandeln sein. Gelegentlich sind die Schleimhäute mitbeteiligt, sodass das Bild einer pluriorifiziellen Ectodermose entsteht.

Komplikationen der Frühreaktion sind selten. Hauptsächlich bei der Calomelkrankheit kommt ein *Meningoencephalismus* vor, sodass die Differentialdiagnose gegenüber einer Masernencephalitis schwierig werden kann. Ferner kann die *Granulozytopenie* alarmierende Grade erreichen und längere Zeit anhalten. Eine richtige *Agranulozytose* haben wir nur einmal erlebt und zwar bei einem seit der Geburt zu Leukopenie neigende Kinde. Ähnlich wie bei der Nirvanolkrankheit und beim Scharlach kann die Calomelkrankheit ungefähr nach 10 Tagen *rezidivieren*. In der Regel hinterlässt die Calomelkrankheit eine »Immunität», gelegentlich gibt es aber ähnlich wie beim Scharlach Zweiterkrankungen nach Jahr und Tag.

Spätreaktionen. Schon bei der Zusammenstellung unserer 59 Fälle von allergischen Reaktionen auf die Quecksilbermedikation im Jahre 1947 (FANCONI, BOTSZTEJN, SCHENKER) ist uns aufgefallen, dass sich eine Feer'sche Krankheit, eine *Akrodynie*, an eine Calomelkrankheit anschliessen kann. Unter unsern in jener Arbeit zusammengestellten 120 Fällen von Akrodynie ging 5 Mal eine Calomelkrankheit voraus und 42 Mal wurden vor Ausbruch der Akrodyniesymptome den Kindern calomelhaltige Wurmmittel gegeben. Seit dieser Zeit fanden wir regelmässig nach Hg-Medikation bei allen unsern Akrodyniepatienten und wir konnten bis Juli 1948 (FANCONI und BOTSZTEJN) in 19 von 20 Fällen eine solche kurz vor Ausbruch der Krankheit nachweisen. Seitdem wurden weitere 4 Kinder ins Spital aufgenommen. Bei allen ging eine Hg-Medikation (3 Mal mit Calomel, einmal mit Hg-Salbe) der Erkrankung voraus. Man begnüge sich nicht nur mit der anamnestischen Angabe, dass kein Hg-haltiges Präparat angewendet wurde, man untersuche den Urin auf Hg-Ausscheidung, denn

bei der enormen Verbreitung von Hg-haltigen Präparaten wissen die Eltern oft gar nicht, ob ein solches gegeben wurde, wie im folgenden

Fall 1. R. Hans. J.-Nr. 7927/48, 1-jährig. Erstes Kind aus gesunder nicht mit Allergosen belasteter Familie. Entwickelte sich bis zum Alter von 7 Monaten ganz normal. Dann im September 1948 schleichender Beginn der Krankheit mit schlechter Stimmung, Schlaflosigkeit, Inappetenz. Das Kind bekam rote kalte Hände, schwitzte sehr viel, auf der Haut traten wechselnde Exantheme auf. Es wurde eine Akrodynie diagnostiziert; nach 2 Monaten erfolgloser Behandlung Spitalaufnahme. Trotz eindringlicher Befragung wurde jede Verabreichung von Medikamenten, insbesondere Hg-haltiger Wurmmittel oder -Salben verneint.

Befund: beim Eintritt am 15.12.1948: klassische Akrodynie. Im Urin von Mitte Dezember kann eine stark vermehrte Hg-Ausscheidung von 270 Gamma pro Liter (Gerichtlich-Medizinisches Institut der Universität Zürich) nachgewiesen werden. Nun wird nochmals energisch nach der Quelle des Quecksilbers geforscht und man bringt heraus, dass wegen Verstopfung am 28.8.48 12 Pulver zu 0.03 Calomel verordnet wurden, davon erhielt das Kind 10 Tage lang $3 \times {}^1/_2$ Pulver pro Tag, anfangs Oktober 1948 erhielt es zudem noch 3—4 Tabl. zu 0.05. Im Ganzen erhielt also das Kind etwa 0.6 bis 0.65 g Calomel = 0.51 bis 0.55 g Hg. Wenn es 2 bis 3 Monate später pro Liter Urin, also in etwa 2 Tagen 0.27 mg Hg ausscheidet, müssen wir annehmen, dass *ein Grossteil des eingenommenen Calomels resorbiert wurde.*

Es handelt sich hier nicht um eine blosse Koinzidenz von Wurmmittel und Akrodynie, denn unter den Kindern von 1—5 Jahren unserer Poliklinik haben nur etwa 30 % überhaupt eine Wurmkur durchgemacht. Ferner konnten WARKANY und wir, neuerdings auch GERARD—LEFÈVRE bei einem Grossteil der Akrodyniepatienten eine stark vermehrte Hg-Ausscheidung im Urin nachweisen. Auch gelang es ELMORE BIVINGS und LEWIS, die Akrodyniesymptome mit BAL-Therapie rasch zum Schwinden zu bringen. Unter unsern 6 mit BAL behandelten Fällen konnten wir jedoch nur bei dreien eine deutliche Besserung erzielen, in den übrigen 3 Fällen blieb jegliche Wirkung aus.

Die Zeitspanne zwischen der Hg-Medikation und den ersten Symptomen der Feerschen Krankheit schwankt zwischen wenigen Tagen und mehreren Wochen: bei erstmaliger Medikation beträgt sie einige Wochen, bei vorbehandelten Kindern nur wenige Tage.

Die Hautproben mit Hg-Salben und Calomel fallen nicht immer positiv aus. Von unsern 8 Fällen des letzten Jahres waren sie 5 Mal positiv und 3 Mal negativ. Es mag sein, dass der Zeitpunkt der Hautprobe im Verlauf der Krankheit eine Rolle spielt ähnlich wie bei der Calomelkrankheit.

Sowohl zum Ausbruch der Calomelkrankheit wie in noch stärkerem Masse der Feerschen Krankheit ist neben dem Quecksilber als exogene Noxe noch eine *besondere Bereitschaft* notwendig, denn nur ein Bruchteil der Kinder, die Hg einverleibt bekommen, erkranken. Bei besonders disponierten Kindern genügen schon minimale Hg-Mengen, um die Früh-, sowie die Spätreaktion auszulösen.

Fall 2. B. Anette, J.-Nr. 7502/48, $1\,^{7}/_{12}$ j. Zweites Kind. Grossvater mütterlicherseits 2 Schübe einer Psychose gehabt. Mutter und deren Schwester leiden an Hypertonie, der Grossvater väterlicherseits an Angina pectoris. Das Kind entwickelte sich normal. Wegen Askaridenabgang wurde im Alter von $1\,^{3}/_{12}$ Jahren ein einziges Santonin-Calomelpulver verabreicht. Im Oktober 1948, 3 Monate später, wurde das Kind verstimmt, schwitzte stark, trotzte, bekam rote Hände und Füsse. Deswegen Konsultation in der Poliklinik, wo man einige Akrodyniesymptome und eine Granulozytopenie von 11 % bei 6 600 Leukozyten findet. Einweisung ins Spital am 22.10.1948.

Befund: Von den Akrodyniesymptomen zeigt das Kind eine leichte Tachykardie von maximal 130/Min. bei normaler Temperatur, Akrocyanose, jedoch keine Schuppung der Hände, Haarausfall, Hypotonie der Muskulatur, keine typische Verstimmung, eher Apathie, das Kind lässt widerstandslos alles mit sich geschehen. Maximaler Blutdruck 95/mm Hg. Die Sternalpunktion ergibt ein zellarmes Mark mit deutlicher Verminderung der Erythropoese (3.5 % Erythroblasten), Vermehrung der Lymphozyten (60.5 %) und der Monozyten (10.5 %), Granulozytopoese nicht wesentlich verändert.

Verlauf (siehe auch Abb. 1): Die Granulozytopenie wird nach wenigen Tagen überwunden, das Kind macht im Allgemeinen den Eindruck einer leichten Akrodynie, insbesondere fällt die Rötung der Hände, der Haarausfall und die Hypotonie auf, sowie die starken Schweisse. Am 3.11. werden Hautproben mit grauer Salbe, 2 %-iger weisser Präcipitatsalbe und Calomelpuder gemacht. Nach 20 Stunden reagiert das Kind mit einem allgemeinen scarlatiniformen Exanthem, Drüsenschwellung, Fieberanstieg. Die Proben fallen stark positiv aus. Zugleich stürzen die Leukozyten und die Granulozyten ohne Schwund der Eosinophilen. Nach 2 Tagen ist die Reaktion überwunden. Im Urin vom 30.10.

kann keine vermehrte Hg-Ausscheidung nachgewiesen werden (weniger als 0.1 Gamma pro Liter). Trotzdem wird eine BAL-Kur durchgeführt. Nach Abschluss der Kur wird die Urinanalyse wiederholt, die Hg-Ausscheidung ist unverändert tief.

Am 29.11. wird eine Hautprobe mit 2 % weisser Präcipitatsalbe wiederholt. Diesmal antwortet das Kind mit starker Lokalreaktion (Abb. 2), hohem Fieberanstieg, Erbrechen. Das Fieber bewegt sich während 3 Tagen zwischen 39 und 40°. Die cervikalen und nuchalen Drüsen schwellen wiederum an, die Milz wird palpabel. Die Leuko- und Granulozyten stürzen auf unternormale Werte, die Eosinophilen verschwinden. Erst mit der Abfieberung tritt ein rubeoliformes generalisiertes Exanthem auf. Das ganze Bild ist einem Exanthema subitum täuschend ähnlich. Nach Überstehen der Reaktion erholt sich das Blutbild rasch, die Eosinophilen erscheinen wieder, eine Blutkontrolle 1 Monat später ergibt vollständig normale Verhältnisse.

Epikrise: Ein $1\,^1/_2$-jähriges Kind erkrankt ca. 3 Monate nach der Einnahme eines einzigen Calomelwurmpulvers an einer etwas atypischen Feerschen Krankheit und Granulozytopenie. Es ist so stark gegen Hg sensibilisiert, dass eine minimale perkutane Quecksilberdosis bei der Hautläppchenprobe genügt, um eine akute Quecksilberkrankheit (Calomelkrankheit) hervorzurufen. Dieses Experiment lässt sich 2 Mal wiederholen. Die Quecksilberüberempfindlichkeit besteht bei diesem Kind, trotzdem das Quecksilber aus dem Körper wahrscheinlich schon ausgeschieden worden war, denn es lassen sich im Urin nur physiologische Spuren des Metalls nachweisen und die zweite »Calomelkrankheit», die wie ein Exanthema subitum verläuft, lässt sich nach beendeter BAL-Kur noch provozieren.

Eine wichtige Rolle spielt das *Alter:* sowohl die Früh- wie auch die Spätreaktion auf Hg kommt hauptsächlich im Kleinkindesalter vor, wahrscheinlich bei den ersten Kontakten mit dem Medikament. Ferner konnten wir bei 44 % unserer Patienten mit Calomelkrankheit und bei 17 % der Akrodyniepatienten (Landolt und Egli) eine Häufung von *allergischen Krankheiten* beim Kind selbst und bei seinen nächsten Angehörigen feststellen. Die Akrodynie befällt ausserdem mit Vorliebe Kinder mit ausgesprochener *vegetativer Labilität,* die noch Jahre nach der Krankheit nachweisbar ist (62 % der Fälle von Landolt und Egli).

Die bis heute vorliegenden Tatsachen berechtigen zur Behauptung, dass das Hg am Ausbruch der Akrodynie eine ganz wichtige Rolle spielt. Ob alle Fälle durch das Hg ausgelöst werden,

bleibe dahingestellt. Das Akrodyniesyndrom könnte ebenso gut durch andere Noxen hervorgerufen werden, ähnlich wie ein der Calomelkrankheit identisches Bild etwa durch Nirvanol oder Luminal usw. ausgelöst wird. Beobachtungen der letzten Zeit lassen vermuten, dass auch nicht so schwere Störungen des vegetativen und psychischen Verhaltens kleiner Kinder (formes frustes der Akrodynie) auf eine Hg-Applikation zurückgeführt werden können.

Da fliessende Übergänge zwischen der Akrodynie und der *Polyradiculitis* bestehen, ist es nicht ausgeschlossen, dass auch letztere als neuroallergische Reaktion auf Hg auftreten kann. Beweise dafür haben wir nicht; in unserm Buche »Die Poliomyelitis und ihre Grenzgebiete» (FANCONI, ZELLWEGER und BOTSZTEJN) haben wir einen Fall von Polyradiculitis anschliessend an eine protrahierte Santonin-Calomelkur ausführlich beschrieben (Fall 27). Zwei Mal entwickelte sich ebenfalls im Anschluss an überdosierte Calomelverabreichung eine klassische, allerdings relativ rasch abklingende Lipoidnephrose (Fall 17 und 18 in FANCONI, BOTSZTEJN und SCHENKER).

Zur Zeit beobachte ich einen Knaben, der nach einer Santonincalomelkur an einer typischen Lipoidnephrose kombiniert mit einer klassischen Akrodynie erkrankt ist. Während nach einigen Wochen die Lipoidnephrose völlig ausgeheilt ist, besteht die Akrodynie in unverminderter Stärke weiter.

Unter dem Eindruck dieser Tatsachen haben wir das Quecksilber aus unserer Medikamentenliste gestrichen. Wir verordnen weder per os noch in Salbenform Quecksilberpräparate — es ist ein durchaus ersetzbares Mittel. Die einzige Ausnahme ist das Mercurochrom, respektive das Merfen, wo das Hg organisch gebunden ist und nicht resorbiert wird. Auch bei starker Hg-Hautüberempfindlichkeit fällt die Probe mit Mercurochrom mit wenigen Ausnahmen negativ aus. Ausserdem haben wir nie eine Hg-Krankheit im Anschluss an die Mercurochromapplikation erlebt, auch wenn diese, etwa bei einer ausgedehnten Verbrenung massiv war.

Summary

Mercury, even in therapeutic doses, frequently causes allergic reactions, particularly in infants. About eight—ten days after mercury has been taken there appears an acute exanthematous reaction, so-called »calomel disease». After weeks or months acrodynia and more rarely a polyradiculitis or a nephrotic syndrome may occur. The acrodynia may be considered a neuroallergic reaction, in which, according to the Zürich school, the mercury usually acts as an allergen (Hapten). This is supported by a positive skin reaction to mercury, shown by Bloch's lip test, in patients with acrodynia, and also by an appreciable amount of mercury in the urine.

Résumé

Le mercure provoque aussi à doses thérapeutiques de très fréquentes réactions allergiques, particulièrement chez le petit enfant. Environ 8 à 10 jours après la prise de mercure apparait la réaction exanthématique aigüe, la »maladie du calomel». Après un délai de quelques semaines à quelques mois il peut se développer une acrodynie, plus rarement und polyradiculite ou une néphrose. L'acrodynie doit être considérée comme une réaction neuroallergique, étant donné que d'après les expériences de l'Ecole de Zürich, le mercure est dans le plus grand nombre des cas l'allergène (haptène). Une preuve en est donnée par l'hypersensibilité cutanée au mercure qui est fréquemment mise en évidence chez les malades atteints d'acrodynie par l'épreuve de Bloch (Bloch'sche Läppchenprobe) et plus tard par la mise en évidence d'une quantité appréciable de mercure dans l'urine.

Zusammenfassung

Das Quecksilber erzeugt auch in therapeutischen Dosen sehr häufig allergische Reaktionen, besonders beim Kleinkind. Etwa 8—10 Tage nach Einnahme des Quecksilbers tritt die akute exanthematische Reaktion, die »Calomelkrankheit» auf; nach Wochen bis Monaten kann sich die Akrodynie, viel seltener eine Polyradiculitis oder ein Nephrosesyndrom einstellen. Die Akro-

dynie wird als neuroallergische Reaktion aufgefasst, wobei nach den Zürcher Erfahrungen weitaus am häufigsten das Quecksilber das Allergen (Hapten) ist. Dafür spricht beim Akrodyniepatienten die häufig mit der Bloch'schen Läppchenprobe nachweisbare Hautüberempfindlichkeit auf Hg, ferner der Nachweis einer beachtlichen Menge Hg im Urin.

Sumario

El mercurio provoca también a dosis terapeuticas muy frecuentemente reacciones alérgicas, particularmente en el niño pequeño. Alrededor de 8 a 10 días después de la ingestión de mercurio, aparece la reacción exantematica aguda, la »enfermedad de calomel». Luego en el termino de algunas semanas a algunos meses puede desarrollarse una acrodinia, y mismo aunque raramente una poliradiculitis o una nefrosis. La acrodinia debe ser considerada como una reacción neuroalérgica, habiendose demostrado por las experiencias de la escuela de Zurich que el mercurio es en la gran mayoria de los casos el alergeno (hapteno). Una prueba de ello sería la hipersensibilidad cutanea al mercurio que se pone frecuentemente en evidencia en los enfermos afectos de acrodinia por la prueba de Bloch (Bloch'sche Läppchenprobe) y más tarde por la presencia de una cantidad apreciable de mercurio en la orina.

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Synchronized Recording of Brain Potentials, Muscle Action Currents, and the Start of Movement in Reaction Time Experiments on Patients with »Chronic» Mental Symptoms After Carbon Monoxide Poisoning

by

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Recent psychological and medical research has begun to pay attention to the possibilities opened up by the electrical recording of brain activity in the study of sensory-motor conduction when synchronized with a registration of certain other phenomena caused by the stimulation of a sense organ under varying conditions. Here I want only to draw attention to BERNHARD's interesting investigation (1940) of the connection between retinal latency with stimulation of different intensities and the so-called »blocking time», i.e. the time that passes between the stimulus and the disappearance of the alpha waves of the electroencephalogram. In a few cases Bernhard has also studied the relation between this time and the motor reaction indicated from the muscle action potentials. In the experiments to be reported here I have partly benefited from Bernhard's experience. In the present research, however, the initial approach to the problem was quite different from Bernhard's, and this also entailed certain differences in the technical arrangements.

The Problem

The experiments were performed Jan.—May 1948 in the EEG-laboratory of Kronprinsessan Lovisa's Children's Hospital in

Stockholm.[1] They were planned as a complement to an investigation of sensory-motor disturbances in cases of »chronic» carbon monoxide poisoning which was carried out during the period 1945—1947 at the Institute of Applied Psychology at the University of Stockholm.[2] From this investigation it had become clear that individuals who on the strength of clinical findings and case history were classified as clear and relatively severe cases of CMP (carbon monoxide poisoning) usually had extremely long reaction times. They also experienced special difficulties in restraining involuntary movement impulses and showed a decreased capacity for motor adjustment and comparatively strong »fatigue fluctuations» after prolonged mental strain.[3]

The *relative* difference in reaction time (RT) between the clinically handicapped and the clinically free subjects was found, surprisingly enough, to be greatest in simple reaction tests (without any choice), and it decreased successively with increasing complexity of the experimental conditions. A closer investigation on this point showed that the time which was required over and above the simple RT to effectuate a choice reaction with two stimuli connected to either response movement was almost as long in the clinically positive group as in the control group, and the same thing applied when the choice was extended to several alternatives. The obvious conclusion is that the factors responsible for the slow motor reaction of the intoxicated subjects do not affect the discriminative and selective mechanisms engaged in

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[1] I wish to take this opportunity of expressing my deep gratitude to the head of the hospital, Professor A. Lichtenstein, M.D., for his kindness in letting me work at the laboratory, and to Dr K. A. Melin, who cooperated in the experiments from the outset and made important contributions to the final decision as to the technical arrangements, and whom I also wish to thank for much valuable advice in the course of my subsequent experiments.

[2] Most of these patients were drivers who were sent to the Institute from a clinic at the Sabbatsberg Hospital in Stockholm especially established during the last war for the treatment of cases affected by producer gas. In the following I shall refer to this establishment as »the Clinic».

[3] The results of these investigations will soon be published in greater detail in a treatise entitled »Reaction Time Experiments with Special Reference to Clinical Applications».

the choice situation. The »central» analysis and rearrangement of the incoming impulses seems, in other words, to take place quite normally, and if there is any question of a brain injury in these cases one must look for it in more afferent or more efferent cortical mechanisms.

The question now arose whether it was possible to go farther on this basis and get a more definite localization of the functional disturbance; it was at this stage of the problem that it struck me that a combination of electroencephalographic recording and measurement of the reaction time might be worth a trial.

Primarily I directed my interest to the electrical response of cortex to light stimulus, as this response may be indicated by the disappearance or »blocking» of the regular alpha rhythm of the brain potentials. A recording of this phenomenon from my pathological subjects might, I hoped, perhaps give a decisive answer to the question whether or not their delayed motor reactions were caused by purely afferent disturbances.[1]

Now it cannot be definitely asserted that the »alpha blocking» ordinarily recorded really does represent an immediate local response from the sensory region of the cortex. As a matter of fact, there are strong grounds for the assumption that we here have also to reckon with a rather long hidden »central period» (BERNHARD 1940), even when the response is taken from the occipital lobe. If, therefore, we should find in some individuals an alpha blocking which is regularly retarded to an abnormal extent, this does not justify the conclusion that the functional disturbance is connected, totally or partly, with afferent mechanisms. But it is equally clear that if we get entirely negative results, i.e. if the »blocking time» remains quite normal even when the motor reaction is extremely slow, then we may exclude every afferent origin of the disorder.

Accordingly I started with some comparatively simple arrangements permitting a rough recording of the alpha blocking on light stimulus in some carefully chosen severe CMP cases and

[1] Actually, certain conditions which will be mentioned in another paper inclined me beforehand to exclude the afferent alternative and assign the origin of the delayed reaction of the CMP cases totally to the efferent side.

some control subjects. In these preliminary experiments no motor reaction was required and the subject, who was comfortably resting on a table in a dark room, was brought into that indifferent state of relaxation which favours the development of a good alpha rhythm in the usual manner.

The results of these experiments were quite negative; no significant difference could be observed between the values for the blocking time in the pathological group and the corresponding values in control subjects with ordinary motor reaction time. This result seemed to confirm the presumption that the great retardation of the motor reaction of the CMP cases could not be ascribed to any mechanism with purely afferent function.[1]

Nevertheless I had to leave the decisive proof to further experiments where the recording of the blocking phenomenon was *directly* combined with a voluntary motor reaction. In the earlier experiments, when no motor response was required, the light stimulus was given to the subject in a neutral state of attention. Obviously the psychological situation will be quite different in a »combined» experiment in which the subject is just waiting for the stimulus, with a strong intention to move a certain limb as soon as it appears. One might suppose that this psychological difference also implies some alterations in the total physiological state and the potential pattern of cortex and consequently also, perhaps, secondarily, an influence on the electrical response as represented in the alpha blocking after a visual stimulation. As already mentioned, this phenomenon cannot generally be assumed to indicate any immediate »reception» response from the sensory field. Consequently, even when we presume that peripheral and conductive nerve-processes are going on in a fixed and automatic way quite independent of the psychological attitude — as a matter of fact even this is very open to discussion — we must nevertheless still ask whether the »central» period of the blocking time is not to some extent influenced by variations in the actual psychological state or attitude of the subject. This question is

[1] Consequently, in my subsequent experiments there was little reason to make a special study, as did BERNHARD (1940), of the »peripheral latency» by means of a separate recording of the electrical response from the retina.

certainly of general theoretical interest. The actual problem, however, was to decide whether the new psychological situation which was introduced by the voluntary reaction tended to break the previously mentioned agreement between normal and pathological subjects.

Concerning the »efferent side», I hoped that the recording of the so-called action potentials in the reacting muscle would give us some relevant criteria. As is well known, the electrical currents which regularly accompany the voluntary innervation of a muscle always start just a short time before the mechanically recorded movement, whether these currents are led off directly by nail electrodes inserted in one or some few motor units or by disk electrodes placed on the skin over the reacting muscle. The values of this »time-lag» in the muscle that have been reported from different quarters vary rather considerably. Usually an interval of about 40—50 msecs is given (e.g. VÖRCHEL 1922, NYSTRÖM 1933), but some investigators have quoted average values up to 100 msecs or even more (HATHAWAY 1935). These variations are obviously to a large extent due to different techniques of registration and to the use of different muscles. But they are probably also caused by constitutional differences in the individuals experimented upon.

There is reason to believe that the interval between the onset of the first action potential and the mechanically recorded contraction in voluntary movements, i.e. the length of the »premotor potential period», is to a large extent determined by the frequency of the action potentials during this period, and since the classical experiment of ADRIAN and BRONK (1929) we know that this frequency is in its turn strongly influenced by the strength of the centrally produced afferent impulses which in this voluntary type of muscle contraction is certainly subject to great individual variations.

It was mainly with these considerations in mind that I decided to include a recording of muscle action potentials in my further experiments on CMP cases. For if we assume their slow motor reaction to be due mainly to some disease affecting the central production or transmission of efferent impulses, we might ex-

pect this to be reflected in a particularly slow and perhaps irregular rhythm of their muscle action potentials during the »premotor» period and thus also in an extension of this particular phase of the total sensory-motor process. As was soon proved, the EEG-apparatus at my disposal was rather suitable for individual comparisons in regard to these criteria.

Technical Arrangements in the »Combined» Experiment

The EEG-apparatus was a 6-channel »Grass» machine (Model 3). Four channels were used for the recording of brain potentials, 1 for the recording of muscle action potentials, and 1 for the marking of light stimulus and motor response. The brain potentials were lead off by five disk-electrodes of the common type. Two of them were placed symmetrically over the occiput, 1 on the top of the skull over the vertex region, and the remaining 2 were fixed at the lobes of the ears and served as indifferent or negative poles. (Both ears were used in order to get a better contact with the body of the subject.) Through this arrangement it was possible to make simultaneous records with the following leads:

1. left occiput—ear (LO—ear);
2. right occiput—ear (RO—ear);
3. vertex—ear (Vert—ear);
4. left—right occiput (LO—RO).

The light stimulus was obtained from a 25 watt gasfilled *Osram lamp* of 24 volts equipped with a particularly thin filament in order to reduce the latency period to a minimum. (It was found necessary to use such a low voltage to avoid widespread field disturbances and thus obtain a distinct mark for the onset of light without overlapping on the brain potential pictures.) The lamp was adapted in a *reflector* spreading the light over a rectangular white-painted *screen* (60 × 40 cm) at a distance of about 250 cm from the eye of the subject (see Fig. 1). As source of current a Nife accumulator of 18 cells was used. Of course this circuit could not be directly connected with the recording appa-

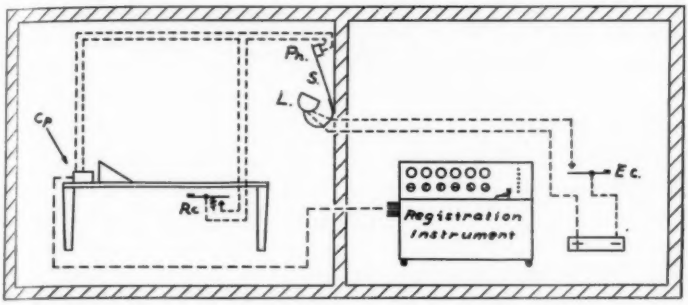

Fig. 1.

ratus. After having tried different condensers and shunt systems, I found that the best solution of this problem was to use a *photo-electric cell* as a secondary source of current. Thus an »EEL Selenium barrier layer cell» was fixed on the back side of the reflecting screen (see Fig. 1, Ph.). The light passed to the cell through a little circular opening in the screen, and the optimal output of the cell was obtained by a simple filter arrangement in front of this opening. When the lamp circuit was established by the *experimenter's key* (Ec) which was placed in the registration chamber, a secondary electric circuit was established from the current produced by the photo-cell, and this current passed through the contact poles of the *reaction key* (Rc) to one of the oscillographs. (These were all connected to a central coupling plate (Cp) placed behind the head of the subject.) Thus a distinct mark was obtained on the record by the corresponding writer. Now, as soon as the subject removed his forefinger from the reaction key, this secondary circuit was broken, and so a new, equally distinct »spike» signal appeared on the same record. For the recording of muscle action potentials it proved quite sufficient for the present purpose to fix one of the active electrodes to the skin over the reacting muscle.

Some typical records obtained with the arrangement described above are reproduced in Fig. 2 (on the next page).

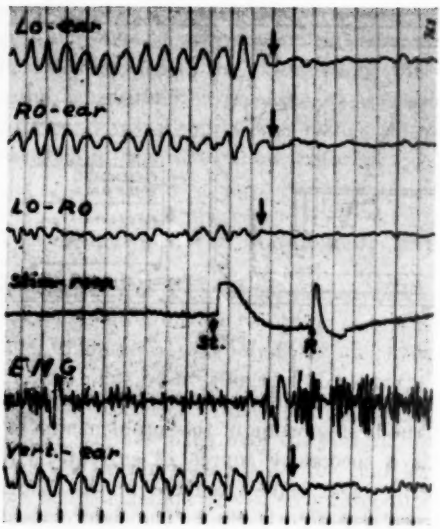

Fig. 2.

Results and Conclusions

As the results of the experiments will be presented and discussed in greater detail in a future paper, I shall give only a short recapitulation of the most interesting items here. Altogether 26 pathological and 20 normal subjects have taken part in the experiment.

1. It was found that the average value for the blocking time from the occipital region remained in all cases within the normal zone whether motor reaction was required or not, and no relation could be established, inter- or intraindividually, between motor reaction time and blocking time from this region. This may be regarded as definite confirmation of the assumption that no purely afferent mechanism is responsible for the delayed motor reaction of the CMP cases.

2. In accordance with earlier investigations (ADRIAN and YAMAGIWA 1935, FREY 1946), the study of the blocking phenom-

enon was here, too, shown to be comparatively difficult from other leads and particularly from the vertex region as compared with the occipital lobe. In fact, distinct blockings could be observed in the vertex region in only 2 out of 26 pathological subjects. In these subjects, however, the phenomenon usually appeared distinctly later from this lead than from any one of the three occipital leads. Such was especially the case in one of them, and this very subject was clinically classified as extremely severe. (This case is represented in the records reproduced above.)

Of course we cannot draw any extensive conclusions from these single cases. They seem, however, rather interesting in the light of the general opinion that the alpha-blocking takes place quite simultaneously in all regions of the intact human skull (see e.g. ADRIAN and MATTHEWS 1934, LOOMIS et al. 1938, BERNHARD 1940). Perhaps in these cases we are confronted with a symptom of some central functional disorder which takes effect only at a comparatively late stage of the sensory motor process.

3. Concerning the electromyographic registration, it may first be pointed out that the interval between the onset of the first muscle action potential and the mechanically recorded movement was significantly greater in the pathological group than in the normal cases. The real difference was not sufficient to explain the abnormal RT values of the CMP cases. However, a closer examination of the recordings has revealed that the prolongation of this »latency» period was intimately connected with a strikingly low frequency of the potentials. If one combines this fact with the conclusions of ADRIAN and BRONK and some later investigators (e.g. HOEFER and PUTMAN 1939, MILES et al. 1947) quoted above, one seems to be justified in interpreting the higher values for this period in the CMP cases as a criterion of a decreased central outflow of afferent impulses, and, consequently, it then seems also rather natural to assume that we are here dealing with some central motor disorder which may be adduced as the real cause of the constant additional time which these people require in all kinds of voluntary motor reaction tests independently of the degree of mental complexity that the test implies.

Summary

This is a preliminary report of some experiments on 26 cases of »carbon monoxide poisoning» with a new arrangement for simultaneous recording of brain and muscle action potentials in combined with a simple motor reaction test with an optical stimulus. In spite of the fact that the motor reaction time was remarkably long in most of these cases, the time for the »blocking» of the alpha rhythm from the occipital region caused by the light stimulus remained within the normal zone in all of them. Thus the delayed motor reaction in the pathological cases cannot reasonably be ascribed to any purely afferent mechanism. On the other hand it was found 1) that the interval between the onset of the first muscle action potential and the mechanically recorded start of the response movement was significantly greater in the pathological group than in the normal and 2) that the prolongation of this interval was intimately connected with an abnormal slow and irregular rhythm of the potentials. In accordance with certain earlier investigations of the relation between the frequence of the muscle action potentials and the strength of the central outflow of afferent impulses in voluntary motor reaction the author is inclined to interpret his results as a confirmation of the general assumption that we are here dealing primarily with some central motor disorders as the real cause of the slow reaction in all kinds of voluntary motor behaviour in »chronic» cases of carbon monoxide poisoning.

Résumé

Ceci est un rapport préliminaire sur quelques expériences de 26 cas »d'intoxication de carbone monoxide» avec un nouvel arrangement pour l'enregistrement simultané du potentiel de l'action cérébrale et musculaire combinée avec un simple examen de réaction motrice par le moyen d'un stimulant optique. Malgré le fait que la durée de la réaction motrice fut d'une longueur remarquable dans la plupart de ces cas, le temps du blocage de l'alpha-rythme de la région occipitale causé par le stimulant lumineux se maintint, dans tous les cas, dans la zone normale. Ainsi, la réaction motrice différée dans les cas pathologiques ne

peut pas, avec raison, être attribuée à un mécanisme purement afférent. D'autre part, il a été constaté 1) que l'intervalle entre le commencement du premier potentiel de l'action musculaire et le départ enregistré par voie mécanique du mouvement correspondant était sensiblement plus long dans le groupe pathologique que dans un cas normal, et 2) que la prolongation de cet intervalle était en rapport intime avec un rythme anormal, lent et irrégulier des potentiels. Conformément à certaines recherches antérieures du rapport entre la fréquence des potentiels de l'action musculaire et la force de l'écoulement central des impulsions afférentes dans l'action motrice volontaire, l'auteur est enclin à interprêter ses résultats comme une confirmation de l'hypothèse générale, selon laquelle nous aurions affaire ici à des désordres moteurs centraux, ceux-ci étant la cause réelle de la réaction lente de toutes sortes de manifestations motrices volontaires dans les cas »chroniques» de l'intoxication de carbone monoxide.

Zusammenfassung

Ein erster Bericht über Experimente bei 26 Fällen von »Kohlenmonoxyd-Vergiftung». Mittels eines neuen Verfahrens der gleichzeitigen Aufzeichnung von Gehirn- und Muskelaktionsströmen wurden einfache motorische Reaktionsversuche durch Lichtreizung beobachtet. Obwohl bei den meisten Fällen die motorische Reaktionszeit bemerkenswert lang war, blieb die Zeit bis zur »Blockierung» des Alpharhythmus der Occipitalregion durch den Lichtreiz bei allen Fällen im Bereich des Normalen. Folglich kann man die Verzögerung der Reaktion in den pathologischen Fällen nicht einfach beim afferenten Leitungsmechanismus suchen. Andererseits fand man,

1) dass das Intervall zwischen dem ersten messbaren Muskelaktionsstrom und dem mechanisch feststellbaren Anspringen der entsprechenden Bewegung bei den pathologischen Gruppen wesentlich länger war als normaliter, und

2) dass die Verlängerung dieses Intervalls eng verbunden war mit einem abnorm langsamen und irregulären Rhythmus des elektrischen Potentials.

In Übereinstimmung mit gewissen älteren Untersuchungs-

ergebnissen über das Verhältnis zwischen Frequenz des muskulären Aktionspotentials und Stärke des zentralen Impulses auf afferente Reize bei willkürlichen motorischen Reaktionen neigt der Autor dazu, seine Resultate als Bestätigung der allgemeinen Annahme aufzufassen, dass die Ursache der verlangsamten, willkürlichen, motorischen Reaktionen aller Art bei »chronischen» Kohlenmonoxyd-Vergiftungen in zentralnervösen Störungen zu suchen ist.

Sumario

Es un informe preliminar sobre algunos experimentos relacionados con 26 casos de envenenamiento de monóxido carbónico, por medio de un arreglo nuevo, a fin de obtener un registro simultáneo de potenciales de la acción del cerebro y del músculo en combinación con una prueba sencilla de reacción motor mediante un estímulo óptico. A pesar de que el tiempo de la reacción motor era notablemente largo en la mayoría de los casos, el tiempo para el »bloqueo» del ritmo alfa desde la región occipital, causado por el estímulo luminoso, quedó en todos los casos dentro de la zona normal. La reacción retardada de los casos patológicos no se puede atribuir razonablemente a ningún mecanismo puramente aferente. Por otro lado se encontró: 1) que el intervalo entre el comienzo del potencial de la primera acción del músculo y el comienzo mecánicamente registrado del movimiento de respuesta eran notablemente mayores en el grupo patológico que en el grupo normal y 2) que la prolongación de este intervalo estaba conectada íntimamente con un ritmo anormalmente lento e irregular de los potenciales. De acuerdo con ciertos estudios anteriores sobre la relación entre la frecuencia de los potenciales de la acción del músculo y la fuerza de la salida central de impulsos aferentes de reacción motor voluntaria, el autor se inclina a interpretar sus resultados como una confirmación de la suposición general de que en este caso nos encontramos primariamente con algunos trastornos centromotores que son la verdadera causa de la acción lenta de todas las clases de funcionamiento motor voluntario en casos crónicos de envenenamiento por monóxido carbónico.

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FROM THE CHILDREN'S DEPARTMENT OF THE UNIVERSITY HOSPITAL LEYDEN.

On Salicylate Poisoning in Children

by

Professor E. GORTER, M. D.

The problem of the exact relation between the administration of large amounts of salicylate and the symptoms observed after it[1] presents many interesting points. I shall discuss these after giving the following case histories.

Case Histories

Case 1. A girl three years of age was admitted into the clinic because the day before between 11 and 12 o'clock she had taken seven, eight, or nine tablets of aspirin. It was not discovered by the parents until 2 o'clock in the afternoon, when the child began to vomit and became dyspnoeic. The family doctor gave charcoal. Vomiting continued the whole night and in the morning the child was somnolent. During the day there was no further vomiting and she took one biscuit and tea.

Urine and stools were normal. The child was very thirsty and presented a deep respiration.

She was the youngest of a large family of seven children.

On admittance we saw a child that was very restless and at the same time somewhat soporous. The respiration was regular but frequent and very deep. Her temperature was 37.6° C., pulse 94, and respiration 30. We did not find any nervous symptoms, although reflexes were somewhat vivid.

The urine contained traces of albumin but not acetone or diacetic acid. The reaction was acid.

Laboratory Findings: hgb. 11 g%, erythrocytes 4 040 000, leukocytes 23 000 with normal distribution. Plasma proteins total 6.3, albumin 4.2, globulin 2.1.

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[1] BARNETT, H. L., et al.: J. Pediat., *21*, 214, 1942. — BYRUM, R. J.: J. Pediat., *33*, 381, 1948.

Total base 170 m.aeq., bicarbonate of the plasma 35 vol.%, pH 7.18, NaCl 670 mg%.

Salicylic acid in the blood: 66 mg%.

Evolution. — The child was treated with intravenous infusions of an isotonic solution of 400 cc. sodium bicarbonate and 150 cc. 5 % glucose.

Discussion. — Thirty six hours after having taken large amounts of aspirin (estimated at 4 g) the child presented the symptoms of salicylate intoxication with acidosis. Although she had polypnoea, she did not show any symptoms of alcalosis, due to the loss of carbon dioxide with the respiration.

Table I shows how the acidosis gradually improved after treatment with large amounts of sodium bicarbonate.

Table I

Date	Blood			
	pH	$NaHCO_3$ vol.%	Total Base	Salicylic Acid mg%
March 19.....	7.18	35	170	66
» 20.....	7.3	43	—	28.5
» 21.....	—	—	156	0
» 22.....	7.4	47		

The temperature was 38.1° C. on the evening of the first day and became normal in a few days. All other symptoms of acidosis disappeared gradually in accordance with the laboratory findings. On admission the urine was strongly acid, pH 5.5. The prothrombin time of the blood was 60 sec. (control 25 sec.); after five hours' infusion 45 sec.

Case 2. A girl three years of age was admitted to the clinic because she had dyspnoea, frequent and deep respiration, was somnolent, and had vomited. She was very thirsty but did not retain the fluid she took. These symptoms had followed the ingestion of a bottle of medicine the morning before at 10.30. Since then she had looked feverish, taken no food, and slept till 2.30 in the afternoon, when vomiting began. Vomiting continued the whole day and night.

The child was very restless and her respiration became deeper and deeper. When she was seen after twenty four hours, her temperature was 38.4° C. Her symptoms did not seem very alarming. She received 250 cc. Ringer's solution with 5 % glucose intravenously.

On admission her urine was acid and contained acetone. The alkali

reserve was 38 vol.% and two days after admission the blood contained 40 mg% salicylic acid.

This child was also slightly anaemic: hgb. 12 g%, erythrocytes 4 million, leukocytes 15 300 with normal distribution.

Evolution. — Symptoms of acidosis and intoxication gradually disappeared (see Table II).

The spinal fluid contained 29 mg% salicylic acid. Cells $^4/_3$, protein 19 mg%, sugar 75 mg% (blood sugar 125 mg%), NaCl 760 mg%.

Table II

Date	Temp.	Blood		Infusion
		$NaHCO_3$ vol.%	Salicylic Acid mg%	
Sept. 20.....	38.4°	38		350 cc
» 22.....	38.1°		40	150 cc
» 24.....	37.9°		0	
» 26.....	37.1°	45		

Urine pH 5.6

Case 3. A boy almost two years of age was sent to us by the dermatological department. He was being treated for a rather severe impetigo and had been given an ointment containing 10 % salicylic acid. The skin on a large part of the scalp and other parts of the body was without covering epidermis. Treatment had been given for three consecutive days.

The first alarming symptoms had appeared the preceding night when the child became very dyspnoeic, with a high fever (40). He was also very restless and sugar, acetone, and diacetic acid in the urine were found. On admittance to our wards we saw a very restless child with very rapid and deep respiration, audible from a distance. Large surfaces of the skin were covered with an impetiginous eczema. Many lymph glands were enlarged.

The urine gave a slight reduction reaction and acetone was strongly positive. The pH was acid 5.5.

The blood bicarbonate was 40 vol.%. The blood contained 90 mg% salicylic acid.

Blood: hgb. 12 g%; erythrocytes 4 250 000; apparently due to the skin infection there was a strong neutrophilic leucocytosis: leucocytes 26 400; neutrophils 67; lymphocytes 29; monocytes 3. As the blood sugar was low, 80 mg%, diabetes could be excluded as a possible cause of the

acidosis. After the discovery of very high amounts of salicylic acid in the blood, there was no longer any doubt that the acidosis was the consequence of a salicylic acid poisoning.

The treatment consisted of infusions of sodium bicarbonate followed by glucose Ringer's fluid. Rapid amelioration of the situation ensued (See Table III).

Table III

	pH	Acetone	Salicylic Acid mg%	$NaHCO_3$ vol.%
14	55	+++	90	40
15	56	++	65	44
17	66	+	0	48
18	78	—		

Case 4. A boy almost two years of age took by mistake seventeen tablets of aspirin, 8.5 g. A few hours later he began vomiting and became so somnolent that his mother succeeded only with difficulty in keeping him awake. The child had never been ill before. *On admittance* he was very restless and had a frequent and deep respiration. His pulse was 124; his temperature 36.8° C. In the urine we found strongly positive acetone reactions and diacetic acid was also present.

Blood: hgb. 11.8 g%; erythrocytes 4 350 000; leukocytes 10 800; with eosinophils 7 %, basophils 1 %, neutrophils 59; lymphocytes 25, monocytes 9.

He received sodium bicarbonate for three days, 1 tsp. thrice a day. Vomiting did not occur after the second day in the hospital. His temperature was 37.7° on the second day and normal afterwards. The respiration gradually became normal in two or three days' time, as did the pulse.

Case 5. A boy four years of age was admitted on May 22. His illness had started ten days before with vomiting, high fever, and a pain in the left side of the thorax. He had received tablets, probably sulfonamide, from the family doctor. Treatment was stopped after five days as it gave no improvement.

On admittance it was soon found that he had a right-sided pleurisy of tuberculous origin.

Evolution. — After ten days' stay in the hospital, he was given aspirin, the first fortnight 2 g per day and thereafter 3 g per day for three weeks. Under this treatment his temperature became normal and

symptoms of the exudate in the pleura less prominent. He remained dyspnoeic, however. After about seven weeks in the hospital, his behaviour became peculiar; he refused to talk to anybody, cried, and was morose. Then his respiration became deep and frequent and his breathing audible from a distance. The frequency of respiration was 24.

As we feared that these symptoms were due to salicylic poisoning, the aspirin was stopped the same day.

Laboratory Findings. On the day of the first symptoms of intoxication, the bicarbonate of the blood was only 25 vol.% CO_2. Total base was 143 m.aeq. per L. Salicylic acid in the blood was 62 mg%. It is worth noting that the salicylic acid could no longer be traced in the blood in a sample taken three days later and that the salicylic acid of the blood taken twenty five days before the first symptoms of poisoning had been eleven mg%. At this time the child had already been receiving 2 g of aspirin daily for eight days. It is highly probable that we could have discovered the approaching intoxication sooner if we had determined the salicylic acid of the blood more frequently, e.g. every week.

Comment

The last observation leads to the conclusion that symptoms of toxicity appear even when the dose of salicylate given to the child has not been so very high. This is in agreement with the results obtained by others who have tried to determine the best dosage of salicylate for the treatment of different diseases.

Dubow and Solomon[1] concluded that a dose of 0.15 g per kg body weight was too high because it produced toxicity in four out of five children two to eleven years of age. On the other hand, 0.100 g per kg body weight was an insufficient dose because the blood level remained too low. The authors therefore proposed the use of a dose of 0.125 g per kg. We may conclude from this study and from other similar ones that there is a small difference between the optimal dose and the dose which produces toxicity. This renders the prescription of salicylate in practice rather troublesome and is a strong argument for introducing the technique of determination of the blood level of salicylate as a routine method during any period when salicylate is prescribed. We must tend to reach a level between 0.030 and 0.035 g%. With this we remain not far from the toxic dose.

[1] Dubow, E., and Solomon, N. H.: Pediatrics, *1*, 495, 1948.

When making these determinations one often observes that a slight fall in the amount of salicylate prescribed produces a relatively large fall in the blood level. Moreover, the prescription of bicarbonate in addition to salicylate may also give unexpected results, insofar as it produces a considerable fall in the salicylate level of the plasma — here also we get lost unless this level is determined.

The explanation of these facts probably lies in the rate of excretion by the kidney. When increasing the dose of salicylate above a certain dose or when adding bicarbonate to the salicylate, one obtains sudden changes in the blood level which can be explained only by admitting changes in resorption or excretion of the salicylate. It is very probable that excretion is the principal factor here, as it has been proved that bicarbonate enhances the excretion of the salicylate.

A salicylate intoxication can be very dangerous if large amounts of a drug are taken accidentally and give a very high blood level. In the preceding case histories we have found numbers as high as 90 mg% and in cases of minor severity we have found numbers as high as 60 mg%. This is also the level that can be found in severe cases on the second or third day, when symptoms have already largely improved.

When prescribing bicarbonate for patients who receive salicylate one has to reckon with the rapid rate of excretion. This bicarbonate has therefore a useful effect only locally in that it prevents lesions of the mucosa of the stomach and the intestine. Without knowing the blood level one has to reckon with a diminished effect on the rheumatism by adding bicarbonate to the salicylate.

Clinical Symptoms. It is very important to be familiar with the first symptoms of salicylate intoxication which may serve to indicate the beginning of an excessively high level of salicylate in the plasma. Among the very first symptoms are paleness, fatigue and drowsiness, and a modification of the respiration. The respiration becomes more frequent and at the same time deeper and can be heard from a distance. When the intoxication becomes more severe we observe that the child becomes restless and

irritable and sometimes drowsy, soporous, or even comatose. Later on symptoms of dehydration appear and at this stage the temperature is certainly high and the pulse very frequent. Generalized convulsions may appear.

Laboratory Findings. We find the symptoms of an acidosis, the pH of the blood is lowered, the carbon dioxide of the plasma is depressed, and there is an excess of acetone and diacetic acid. There is sometimes a prolongation of the prothrombin time. But clinical evidence of haemorrhage is seldom noticed. In severe cases the symptoms of dehydration and slight elevation of non-protein-nitrogen values are found together with albuminuria as well as casts in the urine.

The dosage of salicylate in plasma was not much higher than the level recommended during the treatment of rheumatism. Nevertheless two patients out of thirteen seen by ERGANIAN[1] and associates had a plasma level of 65.2 and 68.5 mg% of salicylate.

Although determinations of salicylate in spinal fluid have been made by several authors, we do not know the level at which severe symptoms make their appearance. The numbers are only one third to one quarter part of the amount in the plasma (ERGANIAN[1]).

There is one factor which has some importance for the evaluation of an acidosis. Some observers have noticed that the deep and frequent respiration tends, all things being equal, to produce an alkalosis by pumping carbodioxide from the blood. As this is very exceptional the majority of authors insist on treating the children from the beginning with alkali and to determine the bicarbonate level of the blood to control this treatment and to prevent secondary alkalosis.

Treatment

Sometimes the general condition of a child who has accidentally taken a large amount of salicylate of aspirin is so poor that immediate anti-shock treatment is necessary. Sometimes also symptoms of dehydration, alone or combined with those of shock,

[1] ERGANIAN, J. A., et al.: J. Pediat., *30*, 129, 1947.

must be dealt with from the beginning. In such cases infusions of plasma, blood, and other fluids are indicated.

The choice of the fluid to be used for the infusions depends largely on the acidosis. We may use a $^1/_6$ molar solution of sodium lactate, which has been advocated by A. F. HARTMANN[1] and is one of the best fluids to prescribe for patients with acidosis. It is also possible to make use of solutions of 5 % glucose in a buffer solution of sodium chloride to which sodium bicarbonate has been added.

It is obvious that by controlling the carbon dioxide, the salicylate level of the blood, and the acidity of the urine one may build a firmer basis for the best treatment of each case. Also, the frequency of the respiration and the pulse may provide useful indications.

Summary

1. The prescription of salicylate for the treatment of various diseases in children must be controlled by regular determination of the salicylate level of the blood.

2. This level must be kept between 30 and 35 mg%. In most cases this result is obtained by prescribing 125 mg salicylate per kg body weight.

3. Administration of bicarbonate has a favourable action only on the mucosa of the stomach but it necessitates prescription of larger doses of salicylate.

4. In cases of severe salicylate intoxication the treatment consists of combatting the acidosis which is always found. In addition treatment of a condition of shock and of dehydration are sometimes necessary.

Résumé

Sur l'intoxication par le salicylate chez les enfants

1) La prescription de salicylate pour le traitement de différentes maladies chez les enfants doit être contrôlée par une détermination régulière du taux de salicylate dans le sang.

[1] HARTMANN, A. F.: J. Pediat., *26*, 214, 1945.

2) Ce taux doit être maintenu entre 30 et 35 mg%. Dans la plupart des cas ce résultat est obtenu en prescrivant 125 mg de salicylate par kg du poids corporel.

3) L'administration de bicarbonate n'a une action favorable que sur la muqueuse gastrique et nécessite la prescription de doses plus grandes de salicylate.

4) Dans le cas d'intoxication grave par le salicylate, le traitement consiste à combattre l'acidose, que l'on peut toujours mettre en évidence. En outre, un traitement du choc et de la deshydratation est quelquefois nécessaire.

Zusammenfassung

Über Salicylatvergiftung bei Kindern

1) Die Verschreibung von Salicylat für die Behandlung von verschiedenen Krankheiten bei Kindern muss durch eine regelmässige Bestimmung des Blutspiegelsalicylates kontrolliert werden.

2) Dieser Spiegel muss zwischen 30 und 35 mg% gehalten werden. In den meisten Fällen wird dieses Resultat dadurch erreicht, dass man 125 mg Salicylat für jedes Kilogramm des Körpergewichtes verschreibt.

3) Die Verabreichung von Bikarbonat hat nur eine günstige Einwirkung auf die Schleimhäute des Magens, aber sie macht die Verschreibung von grösseren Dosen Salicylat notwendig.

4) Im Falle einer schweren Salicylatintoxikation besteht die Behandlung darin, die Acidosis zu bekämpfen, die immer zu finden ist. Ausserdem wird sich manchmal eine Behandlung von einem Schock und einer Dehydration als notwendig erweisen.

Sumario

Intoxicación salicílica en los niños

1. — La prescripción de salicilato para el tratamiento de diversas enfermedades en los niños, debe ser controlada por una determinación regular del nivel de salicilato en la sangre.

2. — Este nivel debe mantenerse alrededor de 30 a 35 mg%. En la mayoria de los casos puede obtenerse este resultado prescribiendo 125 mg por kg de peso.

3. — La administración de bicarbonato tiene solamente una acción favorable sobre la mucosa estomacal, pero requiere la prescripción de dosis mayores de salicilato.

4. — En los casos de intoxicación salicilica severa, el tratamiento consiste en combatir la acidosis que siempre se encuentra. Es a veces además necesario hacer el tratamiento del schoc y de la deshidratación.

FROM THE PAEDIATRIC CLINIC, KRONPRINSESSAN LOVISA'S CHILDREN'S HOSPITAL, STOCKHOLM. HEAD: PROF. A. LICHTENSTEIN, M.D.

Studies of Endogenous Histamine in Clinical and Experimental Hypoxaemia[1]

by

WILHELM GRAF

The amounts of histamine which normally occur in body fluids and tissues show characteristic changes in various pathological conditions. The alterations in blood and tissue histamine met with in anaphylactic and allergic states are well known, as is the raised blood-histamine level following extensive burns.

The mechanisms leading to the release of histamine from cells into the blood or to an increase of tissue histamine are largely unknown, but certain findings point to the existence of a relationship between insufficient tissue oxygenation and the factors influencing the histaminaemia (production and destruction of histamine in the tissues, output of histamine from cells, etc.).

BEST and MACHENRY observed as early as 1930 that histaminase is very sensitive to oxygen deficiency. Subsequent investigations have shed light on this and related questions from different angles. Thus BINET and MARQUIS (1935) found that the histamine content of arterial blood was less than that of venous. BARSOUM and GADDUM (1935) found a raised histamine equivalent in the blood of dogs during reactive hyperaemia and similar evidence was also submitted by ANREP and BARSOUM (1935). BARSOUM and SMIRK (1936) analyzed the blood histamine in cardiac decompensation with stasis and established an increase in the histamine in the erythrocytes, whereas in reactive hyperaemia — secondary to deprive of the arterial blood supply

[1] This investigation received a grant from the Nobel Foundation.

of a region — there was an increase in the plasma histamine. The latter observation has been confirmed by MARCOU, COMSA, and CHIRICEANU (1937) and by ANREP, BARSOUM, SALAMA, and SOUIDAN (1944), among others. BILLINGS and MAEGREATH (1938) also reported an increased release of histamine into the blood stream during reactive hyperaemia. On the other hand, KWIATKOWSKI (1941), as well as EMMELIN, KAHLSON, and WICKSELL (1941) and FOLKOW, HÆGER, and KAHLSON (1948), failed to establish such a mechanism. ANREP, BARSOUM, and TALAAT (1936) reported that the histamine production of the heart in a heart-lung preparation increased during anoxaemia but these authors left the question open whether this increase was real or due to decreased destruction. Investigating the same problem, EISA (1947) found that among other factors, anoxaemia increased the histamine production of the myocardium. Similarly, TARRAS-WAHLBERG (1936) found that in asphyxia the histamine content of the rabbit lung increased.

The effect on blood histamine of lowered oxygen content in the inspired air has been studied by EICHLER, SPEDA, and WOLF (1943), who observed in the cat that respiration in 10 % oxygen elicited an enormous increase in the blood histamine. In a previous work the same authors (EICHLER and SPEDA 1938) showed that hyperventilation of cats induced a decrease in the amounts of histamine extracted from plasma.

BILLIG and HESSER (1944) demonstrated a rise in the blood histamine of human subjects during insulin shock (cf. BARTHELHEIMER and AFENDULIS 1938). The cause, according to the authors, could be the liberation of histamine from injured cells but a contributing factor was sought in reduced inactivation of the histamine produced; the authors quoted do not state, however, that anoxaemia played a rôle in this form of hyperhistaminaemia.

With regard to the influence of anoxaemia on histamine production, the following work by HOLTZ and HEISE (1937) also deserves mention. These authors found that in a Warburg apparatus ground tissue transformed added histidine into histamine. This transformation was the more marked if the process

took place in an atmosphere of nitrogen. Thus HOLTZ (1937) states that a more or less severe oxygen deficiency seems to be an important factor in histamine production in physiological as well as pathological conditions.

Some contradictory evidence may be found in the results obtained by LINDSKOG and GILMAN (1948), who stated that when the lung tissue of the rabbit was deprived of its arterial blood supply by means of ligation, it failed to show a histamine content different from that of normal lung tissue. The conclusion was drawn that a release of histamine does not occur until actual destruction of tissue has taken place. Similarly, RAWLINSON & KELLAWAY (1944), perfusing isolated guinea-pig lungs with a heated saline solution, found no difference between lungs ventilated with air and lungs ventilated with nitrogen, when investigating the histamine content in the perfusate. The authors thus suggest that the absence of increased histamine output means . . . »that anoxia does not cause gross injury to tissue cells».

With regard to the investigations reported above, it seemed of interest to ascertain:

1) whether the blood histamine was raised in conditions characterized by chronic oxygen deficiency.

According to GRAF and MANNHEIMER (1949), cases of morbus caeruleus show on the average 80 % of normal children's values for oxygen consumption and carbon dioxide elimination per liter ventilation and calculated per sq. meter body surface (resting values). Hence such cases might be considered representative of a condition of chronic oxygen deficiency.

2) if the histamine content in the systemic circulation of man increased when the individual was submitted to a period of hypoxaemia. For inducing hypoxaemia the cardiologic hypoxaemia tolerance test devised by MANNHEIMER (1946) was used. The oxygen content of the inspired oxygen-nitrogen-carbon dioxide mixture varied between 7 and 9 %.

Methods

There is considerable diversity of opinion concerning the localization of the histamine extracted from whole blood. Different authors have designated all the corpuscular elements in the circulating blood as carriers of the major proportion of blood histamine. Thus BARSOUM and SMIRK (1936) stated that the red blood corpuscles, unlike plasma, contained fairly large amounts of histamine, a view also shared by MARCOU and GINGOLD (1936). In a series of reports CODE and collaborators (1937—41) presented the theory that the white blood cells of the myeloid series, especially the eosinophils, constituted the main source of the blood histamine. Some observations have furnished additional evidence concerning the relationship between white cells and blood histamine (among others, TINEL, UNGAR & PARROT 1938; KATZ 1940; TANZK 1941; TIERSCH 1947; VALENTINE & LAWRENCE 1948). On the other hand, several authors have failed to confirm the relation between the blood histamine and leukocytosis and/or eosinophilia (BUSINCO and GINUCHO 1938; RANDOLPH and RACKEMANN 1941; NILZÉN 1948). Platelets have also been alleged to be responsible for the histamine effect of blood extracts, viz. by MINARD (1937, 1941) and by ZON, CEDER, and CRIEGLER (1939).

The problem of establishing the precise origin of blood histamine is — as stressed by most authors dealing with the subject — highly complicated by the fact that apparently material differences exist between various species.

With respect to the somewhat doubtful origin of the histamine present in blood, it was considered convenient to use extracts of whole blood in the present investigation.

Histamine Analyses: The histamine assays were carried out with the technique elaborated by CODE as modified from the original method of BARSOUM and GADDUM. Extraction was performed on 5—10 ml heparinized whole blood withdrawn from a cubital vein with the least stasis possible. All values in the present paper are expressed as γ histamine HCl per cc whole blood.

When guinea pig intestine is used for quantitative estimation of the amount of histamine in extracts, certain sources of error must be considered. In addition to the natural variations in a material investigated, there is a dispersion due to technical errors. The resulting dispersion in a series of observations is often considerable, which means that striking differences must be obtained to give a statistical significance. Alternatively the number of observations should be great.

One question that has repeatedly been discussed is whether a certain amount of histidine is transformed into histamine during the extraction procedure ad modum CODE. This has been suggested by ÅKERBLOM (1941) and was shown to be true for horse blood by SCHMITERLÖW (1949), but has not hitherto been confirmed for human blood. On the other hand, EMMELIN, KAHLSON, & WICKSELL (1941) state that no histamine activity was found in CODE extracts of histidine solutions.

In connection with the present investigation 10 mg of d-histidine hydrochloride was treated with trichloroacetic acid extraction, whereafter 2.76 y histamine could be demonstrated in the extract. Apparently, however, it is not exclusively from histidine that histamine can be obtained. In order to prove that trichloroacetic acid extraction can release histamine from complex compounds of a non-physiological character, the following experiment was undertaken. A 1 % solution of histamine was coupled to diazotated benzidine. A coloured, water insoluble product was obtained (analogous to that which — although water soluble — is formed in PAULY's reaction). The precipitate was washed several times. Then 10 mg of the dried substance was treated with CODE's method, upon which 1.80 y histamine was demonstrated in the extract.

In experimental work where groups of experiments are compared, the error involved in possible decarboxylation of histidine may not be of any particular importance, as there seems to be no reason to suppose that systematic differences could originate in this way.

Results

I. Blood Histamine in Morbus Caeruleus

Among the twelve cases listed in *Table 1* all degrees of restricted activity were represented, though none of the patients was actually decompensated. All samples were taken in a resting state except in the case of K. M., who cried and fought vigorously to escape.

Figures for haemoglobin, RBC, WBC, haematocrit, and arterial oxygen saturation are also reproduced in *Table 1*. As can readily be seen, the degree of polycythaemia and cyanosis varied a great deal.

The dispersion of the blood histamine values in this group is considerable, the extreme figures being 0.091 y/cc and 0.640 y/cc, respectively. No relation exists between the blood histamine and the degree of cyanosis. Thus, the high blood histamine values obtained in some of the cases do not correspond to a higher grade oxygen unsaturation. Nor does the blood histamine run parallel with the polycythaemia or the WBC count.

When a normal material of the same age group is considered (*Table 1*, to the right) its lesser dispersion and lower mean value are obvious.

Comment. The difference between the two groups is not statistically significant, amounting only to twice its own standard error. On the other hand, two of the morbus caeruleus values are over 3 σ higher than the mean value of the control group. In the absence of other differences between the two groups this is all that can be stated for the time being.

II. Blood Histamine During Experimental Anoxaemia

The blood histamine was determined in ten healthy male adults (physicians and students, aged nineteen—twenty nine years) before, at the end of and ten minutes after a fifteen minute hypoxia test. *Table 2* gives the results. Only two subjects reacted with a marked increase in the blood histamine. In five cases the hypoxaemia test displayed a higher blood histamine level than the original value; the other five cases actually showed a

Table 1

Blood histamine (in y/cc whole blood) in cases of morbus caeruleus and control cases.

Mb. Caeruleus	Diagnosis	Art 0_2-Sat. %	Hgb	RBC	Hæmato-crit %	WBC	Histamine y/cc	Controls	Blood Histamine in Controls y/cc
Y. E. ♂ 10 yrs	Fallot	*	22.4	7.58	49	5 600	0.640	S. K. ♂ 11 yrs	0.049
G. E. ♀ 12 »	»	80	26.4	8.64	68	8 400	0.194	S. J. ♀ 10 »	0.106
K. K. ♀ 6 »	»	57	20.0	6.30	71	9 000	0.077	K. A. ♂ 9 »	0.130
B. K. ♀ 10 »	Eisenmenger	76	19.5	5.98	52	7 200	0.110	S. W. ♂ 10 »	0.092
B. A. ♂ 10 »	»	79	22.8	6.52	61	6 200	0.076	R. N. ♂ 10 »	0.081
M. M. ♀ 17 »	»	67	17.2	5.02	46	4 800	0.071	G. J. ♀ 12 »	0.096
O. H. ♂ 26 »	»	92	16.1	4.67	50	6 200	0.160	K. T. ♂ 14 »	0.093
A. E. ♀ 18 »	Fallot	76	24.4	7.48	75	5 200	0.072	R. I. ♂ 13 »	0.120
R. S. ♂ 4 »	»	78	24.4	6.38	59	6 000	0.142	K. F. ♀ 10 »	0.105
E. L. ♂ 2 »	»	46	15.9	4.98	52	11 000	0.330	G. T. ♂ 6 »	0.088
G. H. ♀ 6 »	»	*	19.2	5.68	60	11 600	0.261	U. D. ♂ 9 »	0.075
K. M. ♂ 9 »	»	84	13.2	4.08	38	9 800	0.083	A. C. ♂ 6 »	0.075
						M	0.185		0.091
* No reliable value obtained.						σ	0.159		0.072
						ε	0.046		0.021
						n	12		12

Difference = 0.094 ± 0.051.

Table 2

Blood histamine (expressed in y/cc whole blood) before, at the end of, and following hypoxia test.

Subject	Histamine Before Test	End of 15 Min. Hypoxia Test	10 Min. After End of Test
W. G. 28 yrs	0.050	0.060	0.060
P. Ö. 20 »	0.098	0.667	0.104
G. Z. 22 »	0.140	0.150	0.090
B. F. 20 »	0.200	0.180	0.080
T. H. 28 »	0.158	0.315	0.195
H. T. 29 »	0.119	0.040	0.038
C. E. 23 »	0.046	0.047	0.067
U. S. 20 »	0.067	0.009	0.045
C. M. 19 »	0.020	0.013	0.008
U. F. 23 »	0.047	0.045	0.075
M	0.095	0.154	0.076
σ	0.073	0.195	0.047
ε	0.023	0.062	0.015

D 0′—15′ 0.059 ± 0.065.
D 15′—25′ 0.078 ± 0.064.

decrease. Thus the mean values do not give a significant difference between the normal state and the hypoxaemic state, but two of the hypoxæmia values exceed the mean value before the test by more than 3 σ, indicating that in these cases an increase really occurred. These two cases did not show lesser tolerance of the hypoxaemia test or more conspicuous cyanosis than the rest, nor was there any other sign of general distress. Consequently the blood histamine increase failed to correspond to the general reaction to the test, which was rather uniform with the 7—9 % oxygen used.

In 50 % of the cases the hypoxia blood histamine was lower than that before the test. It is possible that a transitory increase had already occurred here, followed by decreased values. The decrease in the different cases was, however, not greater than can be ascribed to the dispersion.

The mean value after the test (ten minutes after returning to air respiration) was slightly lower than it was before the test.

There was striking correspondence between the mean value for healthy children (*Table 1*, to the right) and that for the normal adults (*Table 2*, Column 1), the means being 0.091 ± 0.021 and 0.095 ± 0.023 y/cc, respectively. These figures also show good conformity with those of other authors: ROSE and BROWNE (1940) report the mean value 0.040 y/cc (fifty subjects) and NILZÉN (1947) arrives at the mean value of 0.060 y/cc (thirty subjects). Both these figures are expressed as histamine base, corresponding, respectively, to 0.067 and 0.100 y/cc histamine HCl. Small differences in the normal figures for blood histamine reported by different authors might be explained by impurities in the histamine dihydrochloride substance used for the standard solutions or by differences in the reactivity of the intestine in different races of guinea pig; even seasonal, sex, and body weight variations have to be considered.

Comment. If a blood histamine increase is to be induced in all the cases tested, it seems probable that a more profound cyanosis is required than is elicited by 7—9 % oxygen respiration over a period of fifteen minutes. Thus in a state of moderate cyanosis man does not seem as likely to react with a blood histamine increase as does, at least according to EICHLER, SPEDA, and WOLF (1943), the cat.

On the other hand, it may also be assumed that in the cases in which the result of the test was negative, the histamine level had really been raised, but the effect was too transient to be demonstrated within the fifteen minute period used. In experiments on reactive hyperaemia ANREP et al. (1944) found that a blood histamine increase followed by a rapid return to normal figures can occur within one—two minutes. In EICHLER, SPEDA, and WOLF's experiments on hypoxaemia, however, a positive result was still found after ten minutes of hypoxaemia. In addition, some of the cases in Table 2 which were sampled also after five minutes of hypoxaemia showed values within the normal range.

III. The Histamine Content of Suffocated Animals

In connection with the hypoxaemia experiments, it was considered interesting to determine using a species other than man whether a profound anoxaemia causes a real increase in the histamine amounts throughout the body or whether the increase in the blood noticed by e.g. EICHLER, SPEDA, and WOLF (1943) and in some of the author's experiments is due only to an increased release of preformed histamine from body cells. EICHLER, SPEDA, and WOLF state that when a cat is submitted to hypoxia the initial increase in the blood histamine is due to depletion of the histamine stores, and that it is also for this reason that later on the blood histamine drops to subnormal values.

A simple and suitable arrangement for studying this problem was found in the submission of small animals, such as mice, to lethal anoxaemia by suffocation followed by determination of the amount of histamine which could be extracted from the whole animal. This technique of evaluating the histamine content of whole mice was used previously by ALEXANDER (1944) and by DEKANSKI (1945).

A series of untreated control animals were killed by crushing their necks and then cut in small pieces. These pieces were then »homogenized» to a fine suspension by means of a drill fitted in a cylindrical steel case and rotating at about 1 000 tours/min. The histamine content of the normal mice in the present investigation (see *Table 3*) was somewhat lower than the figures reported by DEKANSKI (1945). If the mean to the left in *Table 3* is transferred into histamine base a value of 4.5 y/g is obtained; the average histamine content (calculated as base) of DEKANSKI's mice was 216 y, making with a body weight of 20—30 g a y/g figure of 7.2—10.8. The histamine content of normal mice in ALEXANDER's (1944) material was 190—410 y, making 6.0—7.0 y/g body weight (expressed as base?).

Another group of animals were suffocated two at a time in a flask with a volume of 1 700 ml. They generally consumed the oxygen two—three hours after having been closed up in the flask. As soon as they were dead they were treated in the same manner as the controls.

Table 3

Histamine content of normal and suffocated mice.

Normal Animals			Suffocated Animals		
Weight g	γ Histamine in Whole Mouse	γ Histamine per g Weight	Weight g	γ Histamine in Whole Mouse	γ Histamine per g Weight
1. 20	190.0	9.5	1. 25	295.0	11.8
2. 18	199.8	11.1	2. 16	300.8	18.8
3. 12	50.0	4.2	3. 14	311.4	25.1
4. 16	100.0	6.3	4. 15	227.0	15.8
5. 16	100.0	6.3	5. 27	375.3	13.9
6. 19	182.9	9.6	6. 21.3	696.2	29.4
7. 16	174.4	10.9	7. 26	686.4	26.4
8. 21.5	118.3	5.5	8. 19	687.8	36.2
9. 21	97.7	4.7	9. 21	394.8	18.8
10. 19	127.3	6.7	10. 26	686.4	26.4
			11. 23	656.3	28.6
			12. 20	349.8	17.5
M 17.9		M 7.5	M 21.1		M 22.4
		σ 2.4			σ 7.0
		ε 0.8			ε 2.0

Difference 14.9 ± 2.2.

Table 3 gives the histamine contents of the controls and the suffocated animals, respectively. The histamine content calculated in y per g body weight was increased about threefold in the suffocated animals. The difference between the two groups has a statistical significance of $P < 0.001$.

Comment. Thus the anoxaemia brought about by slow suffocation cannot only have the effect of transient liberation of preexisting histamine. On the other hand, determination of the extent to which the high histamine content of the suffocated mice is due to increased production and decreased destruction, respectively, requires further study.

Summary

1. In congenital heart disease with cyanosis (tetralogy of Fallot, Eisenmenger complex) high blood-histamine values occur, though they do not give rise to mean values significantly different from those of healthy acyanotic children of the same age. Out of twelve morbus caeruleus cases two yielded values over 3σ higher than the mean value of the control group. These high values displayed no correlation with the degree of cyanosis or polycythaemia.

2. The blood histamine level of normal children was identical with that of healthy adults. The means of the groups were 0.091 ± 0.21 ($n = 12$) and 0.095 ± 0.023 ($n = 10$) y histamine HCl/cc whole blood, respectively.

3. Ten healthy adults submitted to a fifteen minute cardiological hypoxia test with 7—9 % oxygen displayed no significant rise in the blood histamine at the end of the test, although two subjects showed values over 3σ higher than the mean value before the test.

4. Mice suffocated slowly to death showed a histamine content per whole animal which, calculated per g body weight, was three times as large as that of normal animals.

5. Small amounts of histamine were demonstrated when trichloroacetic acid extraction was performed on 10 mg of d-histidine and on 10 mg of a compound obtained by coupling histamine with diazotated benzidine. Such errors are, however, not considered serious when the method in question is used for purposes of comparison.

Résumé

1. Dans les maladies cardiaques congénitales avec cyanose (tétralogie de Fallot, complexe d'Eisenmenger) se présentent des valeurs histaminiques du sang d'un degré élevé sans toutefois amener une valeur moyenne sensiblement différente de celle des enfants acyanotiques du même âge. Sur 12 cas de morbus caeruleus deux rapportèrent des valeurs de plus de 3σ au dessus de la moyenne du groupe contrôlé. Ces hautes valeurs ne pré-

sentaient aucun rapport avec le degré de cyanose ou de polycythémia.

2. Le niveau histaminique du sang des enfants normaux était entièrement identique à celui des adultes en parfaite santé. La moyenne des groupes fut 0.091 ± 0.21 ($n = 12$) et 0.095 ± 0.023 ($n = 10$) y histamine HCl/cc total du sang respectivement.

3. 10 adultes en bonne santé soumis à un examen d'hypoxia cardiologique de 15 minutes avec 7—9 % d'oxygène ne présentèrent aucune augmentation importante de l'histamine du sang à la fin de cet examen, bien que deux sujets se soient présentés d'une valeur de plus de $3\,\sigma$ au dessus de la moyenne d'avant l'examen.

4. Des souris, lentement étouffés, montrèrent un contenu d'histamine de toute la bête qui fut calculé par g, poids du corps, trois fois plus élevé que celui des bêtes normales.

5. De petites quantités d'histamine furent démontrées lors d'une extraction trichloroacétique acide exécutée sur 10 mg d-histidine et 10 mg d'une composition obtenue par le mélange d'histamine et de benzidine diazotée. De telles erreurs ne sont cependant pas considérées comme graves lorsque la méthode en question est employée à titre de comparaison.

Zusammenfassung

1. Bei kongenitalen Herzkrankheiten mit Cyanose (Tetralogie von Fallot, Eisenmenger-Komplex) treten im Blut hohe Histaminwerte auf, jedoch nicht von solcher Höhe, dass man sie als Unterscheidungsmerkmal gegenüber gesunden, nicht cyanotischen Kindern gleichen Alters verwerten könnte. Zwei von 12 Fällen mit Morbus caeruleus zeigten Werte von mehr als $3\,\sigma$ über dem Durchschnittswert der Kontrollgruppe. Diese Histaminzunahme steht jedoch in keinem Verhältnis zum Grad der Cyanose oder der Polycythämie.

2. Der Histaminblutspiegel normaler Kinder war vollständig identisch mit dem gesunder Erwachsener. Die Durchschnittswerte der Gruppen waren 0.091 ± 0.21 ($n = 12$) und 0.095 ± 0.023 ($n = 10$) γ (Gamma) Histamin HCl bezogen auf 1 ccm des Gesamtblutes.

3. 10 gesunde Erwachsene, die einem cardiologischen 15 Min. Hypoxämietest mit 7—9 % Sauerstoff unterzogen wurden, liessen am Ende des Testes keine bemerkenswerte Erhöhung des Bluthistamins erkennen, obwohl zwei Versuchspersonen Werte von mehr als 3 σ über dem Durchschnittswert vor dem Versuch aufwiesen.

4. Bei Mäusen, die durch langsamen Luftentzug getötet wurden, war der Histamingehalt im ganzen Tier drei Mal so hoch als bei normalen getöteten Tieren (berechnet auf g Körpergewicht).

5. Es konnten kleine Mengen Histamin extrahiert werden, wenn Trichloressigsäure sowohl auf 10 mg d-Histidin als auch auf eine Verbindung einwirkte, die durch die Verkettung von Histamin mit Benzidin-Diazotat entstand.

Solche Irrtümer werden jedoch nicht als schwer betrachtet, wenn die fragliche Methode für Vergleichszwecke angewendet wird.

Sumario

1. En enfermedades congénitas del corazón con cianosis (tetralogía de Fallot, complejo Eisenmenger) se presentan altos valores de histamina de sangre, aunque no dan origen a un valor mediano que sea expresivamente distinto del de niños acianóticos de la misma edad y de buena salud. De un grupo de 12 casos de morbus caeruleus, dos dieron valores que eran más de 3 σ veces más altos que el valor mediano del grupo controlado. Estos altos valores no tenían correlación con el grado de cianosis o policitemia.

2. El nivel de histamina del corazón de niños normales era exactamente idéntico al de los adultos sanos. Los valores medios de los grupos eran 0.091 ± 0.21 ($n = 12$) y 0.095 ± 0.023 ($n = 10$) e histamina HCl/cc de sangre llena, respectivamente.

3. 10 adultos sanos fueron sometidos a una prueba de 15 minutos de hipoxia cardiológica con 7—9 % de oxígeno y no presentaron ningún aumento importante de la histamina de sangre al final del ensayo, aunque dos sujetos mostraron valores que eran 3 σ veces más altos que el valor mediano antes del ensayo.

4. Los ratones, que fueron sofocados lentamente hasta la muerte, mostraron un contenido de histamina en todo el cuerpo, el cual era, calculado en gramos por peso de cuerpo, tres veces mayor que el de los animales normales.

5. Se observaron pequeñas cantidades de histamina cuando se ejecutó la extracción de ácido tricloroacético de 10 mg de d-histidina y de 10 mg de un compuesto que se obtiene mezclando histamina con bencidina diazotada. Los errores de esta clase no se considera, sin embargo, que sean de importancia cuando el método en cuestión se usa para fines comparativos.

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Diabetes Mellitus in Early Infancy, Treated without Dietary Restrictions[1]

by

GEORGE M. GUEST, M.D.

In this volume dedicated to honouring Professor Lichtenstein, I should like to describe the unusual occurrence of diabetes mellitus in 3 young infants[2], successive siblings, and to discuss some of the experiences we have had in the Cincinnati Children's Hospital in the management of diabetes in infants and children with an »unrestricted» dietary regime. Our practice of this regime has been generously guided by Professor Lichtenstein's writings, and encouraged by a visit he made to this clinic in 1947 when he saw the infants whose records form a part of this report.

In the family history of the cases here reported it is noteworthy that diabetes has occurred in collateral branches of both the father's and the mother's families and that a first cousin of the infants, also enrolled in our clinic, developed diabetes at the age of $3\,^1/_2$ years. The father and mother of the infants are apparently not diabetic. Their first-born child, a girl now 11 years of age, is healthy, non-diabetic.

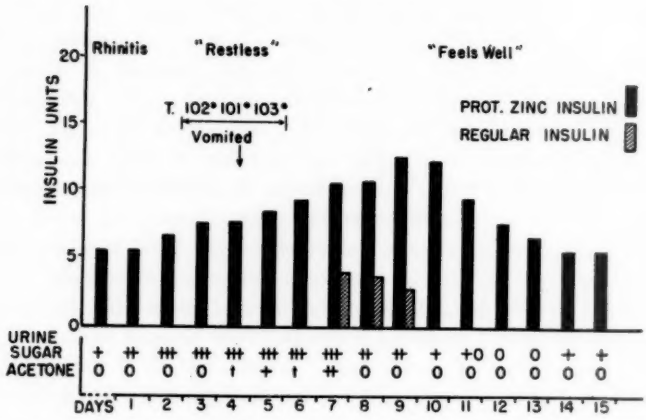
Diabetes was discovered in the second child, a girl, when in 1942 at the age of 3 months she was admitted to the hospital with a tentative diagnosis of upper respiratory infection, with fever, vomiting, and labored breathing. After the discovery of glycosuria,

[1] Studies partially supported by a grant-in-aid from the Nutrition Foundation, Inc., New York.

[2] A preliminary report on these cases was delivered at the meeting of the American Pediatric Society, Stockbridge, Mass., May, 1947 (Transactions, Am. J. Dis. Child., *75:* 461, 1948).

chemical examination of the blood revealed: sugar 1156 mg %; serum CO_2 content 12.5 vol. %; serum pH 6.96; urea nitrogen 50 mg %. She died about 14 hours after the diagnosis of diabetic acidosis was made. After the administration of insulin and parenteral fluids values for the sugar, CO_2, and pH of the blood came to within a normal range before she died, but no urine was passed during the last 8 hours. In retrospect it appeared that she had been severely acidotic more than 48 hours, possibly 72 hours, before appropriate treatment was started. The fatal outcome was probably accounted for by the prolonged period of acidosis.

B.B., the third child, male, was born at home May 16, 1945. He was partially breast fed 2 months, then weaned because of a diminishing flow of breast milk. At the age of 3 months the mother noticed increasing polyuria and brought him to the hospital, where sugar was found in the urine. Well-developed and well-nourished, the baby then appeared to be healthy except for a mild respiratory infection, 3-plus glycosuria, and mild acetonuria. The family physician had examined 2 samples of urine, at 1 week of age and about a week before the hospital admission, and found both sugar-free. During a 24-hour period of observation in the hospital before insulin was administered the blood sugar was determined at 2-hourly intervals and was found varying from 215 to 525 mg per 100 cc. The CO_2 content of the blood serum and other chemical data were within the normal range. Administration of insulin was followed by prompt cessation of acetonuria and diminution of glycosuria. Satisfactory regulation was attained at first with a mixture of protamine zinc and regular insulin, 10 and 6 units, respectively, given once a day. With diminishing glycosuria the dose was reduced progressively to only 2 units at the end of 10 days. Subsequently he developed a series of furuncles and the insulin requirement increased for a time to between 5 and 15 units. He was sent home at 4 months of age, receiving around 5 units protamine zinc insulin daily, a dose that allowed continuous mild glycosuria. A normal infant's diet of evaporated milk formula was prescribed, with cereal, egg, vegetables, and other foods offered at the usual ages in amounts to be governed largely by his appetite. The subsequent course has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"Feels Well"
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Fig. 1. Infant B.B. at age of 7 months. Regulation of insulin dosage at home during a mild respiratory infection.

been fairly uneventful except for several episodes of mild respiratory infections, and mumps at the age of 2 years. With each of these episodes the mother on her own initiative sharply raised the insulin dosage at the appearance of increasing glycosuria and acetonuria, and reduced the dosage promptly as glycosuria diminished with recovery (See Figure 1). The feeding schedule followed the usual practices for infant's feeding in this clinic, as will be discussed in further detail later. At present he receives approximately 8 units of protamine zinc insulin and 6 units of regular insulin, mixed, in a single injection each morning. During the $3\frac{1}{2}$ years since the onset of diabetes the urine has rarely been sugar-free. Growth has been normal, and the infant has never been in acidosis.

Figure 1 represents an example of successful home management of changes in insulin dosage during an episode of mild respiratory infection in the infant B.B. at the age of seven months. This chart was constructed from the mother's own record, kept between bi-weekly visits to the clinic. At one visit, on the first day indicated in the chart, the child showed signs of developing a slight cold. For some time he had been receiving

6 units of protamine zinc insulin daily and showing only about 1-plus glycosuria most of the day, with no acetone, while eating the recommended normal infant diet largely according to appetite. During 3 following days the rhinitis increased, he developed fever, with temperature from 101° to 103°, and vomited once. Noting the increasing glycosuria the mother increased the insulin dose to 8, 9, and then 10 units, and then, with appearance of a strongly positive acetone test, to 13 units protamine zinc insulin with 4 additional units of regular insulin. The acetonuria ceased promptly, and as the temperature became normal the next day the glycosuria diminished. The insulin dose then was decreased gradually over a period of 5 days, with the added regular insulin given only 3 days. At the time of the next clinic visit, at the end of 2 weeks, the usual daily dose of 6 units was being given, with glycosuria only 1-plus and no acetonuria. The period of increased dosage had covered 12 days. This episode is typical of many in our records, showing how increasing needs for insulin during infections were recognized at home, and how a sharply increased dosage of insulin served to avert the almost certain development of acidosis with its attendant complications.

D.B., the fourth child, male, was born at home January 3, 1947. The parents tested the urine of the baby on the first day and daily thereafter, obtaining urine samples by squeezing the diapers. The mother had abundant milk and nursed the baby about every 3 hours. A trace of glycosuria was first found on the ninth day. The test was negative in the morning of the tenth day but was 1-plus in the afternoon and increased to 3-plus that evening. On the eleventh day he was brought to the hospital. The infant then appeared to be quite well in every way except for the glycosuria and slight acetonuria. In the hospital he was placed on an evaporated milk formula given by bottle every 3 hours. Blood sugar determinations were made every 2 hours for 24 hours before insulin was started and afterwards at intervals as shown in Figure 1. The blood sugar level was 456 mg % initially and fluctuated between 330 and 576 mg % during the first 24 hour period. Other blood chemical data were normal.

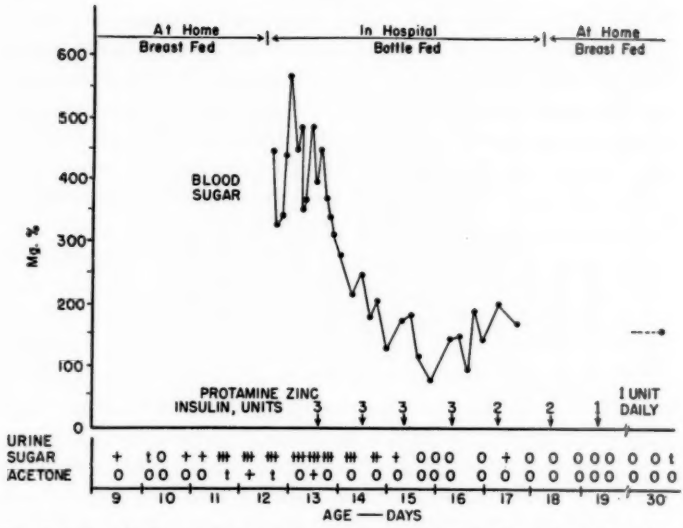

Fig. 2. Infant D.B., born January 3, 1947. Urinary findings from the ninth day of life when glycosuria was discovered; blood sugar levels during 24 hours before and 5 days after the start of insulin therapy.

Acetonuria was present at the time of admission; it was absent at midnight of the twelfth day at the time the blood sugar rose to the highest level, 576 mg %, but reappeared the next morning. A first dose of 3 units of protamine zinc insulin was given the afternoon of the second hospital day, i.e. the thirteenth day of age. The blood sugar level then fell progressively from around 400 to around 200 mg % and the acetonuria promptly disappeared. Continued daily doses of 3 units of protamine zinc insulin brought the blood sugar to between 100 and 200 mg % on the third and fourth days of treatment, and the urine became sugar-free. The dose was reduced to 2 units on the fifth day and the baby was sent home on the sixth hospital day, to be breast-fed with 1 bottle supplementary feeding and to receive 1 unit of protamine zinc insulin daily. The bottle supplement was stopped after about 10 days. With feedings offered on a demand schedule the baby at about 6 weeks of age settled on 4 breast feedings a

day, sleeping soundly through the night. Occasional weighings before and after nursing indicated that he received about 750 cc. (20 to 25 oz.) of breast milk per day. Orange juice and oleum percomorphum were started at 2 weeks; cereal was offered at 3 months, egg at 3 1/2 months, strained vegetables at 4 months, liver at about 5 1/2 months; chopped vegetables at 8 months. After breast feeding was stopped at 10 months he received an evaporated milk formula. His weight was 7.5 kg at 5 months (double the birth weight), 10 kg at 1 year, and 13.1 kg at 18 months. He suffered several minor colds and mumps at 17 months, with little evidence of metabolic disturbance. Vaccination and immunizations to diphtheria, tetanus, and pertussis were performed at 4 to 6 months. Insulin dosage was increased from 2 units a day to 6 units a day at 10 months, shortly after weaning. At the age of 21 months he is receiving protamine zinc insulin 8 units and regular insulin 6 units, in a single injection, daily.

In addition to these sibling infants, 6 other cases of infantile diabetes in which the disease was recognized before 2 years of age have been observed in this clinic during the past 10 years. 3 boys the onset of whose symptoms occurred at 7, 10, and 11 months of age, respectively, are now 10, 9, and 7 years old. 3 girls the onset of whose symptoms occurred at 20, 21, and 23 months, respectively, are now 10, 9 1/2, and 7 1/2 years old. Each of these infants was at first cared for with prescribed measured diets, with insulin dosage adjusted to keep their glycosuria minimal, according to usual practices that were followed in the clinic until the years 1942 to 1945 when the free diet was first tried among other patients and gradually adopted for all. During the past 4 or 5 years these 6 patients have followed the unrestricted dietary regime, with insulin dosage adjusted to permit continuous mild glycosuria. At the time of their change from measured to unmeasured diets there was little or no significant change in daily insulin dosage beyond what is expected with advancing age. At present each of the children is taking between 20 and 30 units (total) of insulin per day. Their growth is good, hospitalization for any cause has been rare, and even mild insulin reactions are uncommon. It should be noted that 3 were in

severe acidosis when their disease was first recognized. Only 1 of the children has been hospitalized for acidosis (and in that case only once) since treatment was started.

Discussion

The fundamental principles that govern diabetic care are of course the same for infants as for older patients. But, particularly for the parents who care for the young diabetic patient at home, there are many special problems peculiar to infancy that merit special attention, problems that diminish in magnitude as the child grows older. In the young infant various metabolic factors, endogenous and exogenous, make for instability of the carbohydrate regulatory mechanisms. Hypoglycemic reactions induced by too much insulin are less easily recognized in the infant than later when the child is ambulatory and talking, and the adjustment of small doses of insulin is often difficult. The procurement of urine samples for frequent testing, essential for the regulation of insulin dosage, is a practical problem of much concern for the parents.[1]

Two main schools of thought at the present time dictate certain sharply opposed practices in diabetic care. The arguments of one school, favoring a »prescribed-diet-aglycosuric regime», are based mainly on the proposition that hyperglycaemia is unphysiologic and ultimately may be responsible for the more severe complications of the disease. Arguments of the other school, favoring a »free-diet-glycosuric regime», are based on counterpropositions that mild hyperglycemia per se is not harmful, and that more serious metabolic disturbances attend the development of ketosis and acidosis. Under the latter concept, absence of acetonuria is held to be a more important criterion of insulin-

[1] For collecting urine samples from small infants without using cumbersome tubes, a convenient device is a small shallow paper cup containing a wad of absorbent cotton placed inside the diaper. The paper cup prevents to some extent the spread of urine into the diaper, and the wad of cotton when squeezed out yields easily enough urine for sugar and acetone tests. The diaper itself similarly may be squeezed out, if taken immediately after urination occurs — but this requires more watchfulness.

control than the amount of sugar in the urine, especially for purposes of self-management by the patients at home. During the past ten years this controversy has involved much contradictory and sometimes acrimonious debate. With regard to juvenile diabetes, the controversy actually is concerned mainly with the relative significance of glycosuria and hyperglycaemia, since even those who attempt to maintain aglycosuria most rigidly prescribe generous »normal» diets for diabetic children (JACKSON AND BOYD; JACKSON AND KELLY). The measurement of the diets then is required only for making easier the daily regulation of insulin dosage to avoid insulin reactions. It should be noted, parenthetically, that the free-diet-glycosuric regime has been tried much less widely in the United States than in Scandinavian and European countries. TOLSTOI in New York has reported favourable results in the treatment of adults on such a regime since about 1939, but comparatively few others have followed this lead. Opponents of this regime predict that cardiovascular disease, which occurs so commonly as a late complication of diabetes, will be aggravated by long-continued hyperglycaemia even though the patients seem to do well and suffer no immediate ill effects. This claim of course can be supported or refuted only by long-continued comparisons of the end-results of the two systems of management. In the meantime, practical advantages of the liberal regime must be weighed against objections — theoretical and otherwise — that are raised against it.

In our experience, the unrestricted dietary regime has important advantages in allowing maximal freedom for the diabetic child to lead a normal life. For both parents and children, the psychological difficulties of regimentation and implications of invalidism which often attend adherence to a strictly prescribed diet are minimized, the inconveniences of measuring a special diet are avoided, and worries over the occurrence of hypoglycaemic reactions are reduced. The latter is an especial advantage in the handling of very young infants. The adjustment of insulin dosage to permit continuous glycosuria is a safeguard against hypoglycaemic reactions when the food intake is less than usual or when there is unusual exercise; on the other hand, when hunger may

be a symptom of impending hypoglycaemic reactions the freedom to eat without restriction is also a safeguard.

The general plan for diabetic care now recommended in our clinic follows closely the lines indicated by LICHTENSTEIN and by STOLTE, and can be described very briefly. Advice to the parents of diabetic children regarding diet is essentially the same as is offered for non-diabetic healthy children. Printed forms indicating the sample diets recommended at different ages for normal children are given for guidance, with emphasis on the inclusion of adequate quantities of natural foods to cover all requirements for growth and energy, with the usual vitamin supplements. The child is allowed to eat of the family's meals, according to appetite, within the same generous limits of choice as non-diabetic children enjoy. Sweets in reasonable amounts are allowed, with restrictions only to avoid overindulgence by standards that should apply to non-diabetic children. It is emphasized that the words »free» or »unrestricted» are used to indicate an unmeasured diet, more or less self-selected with regard to amounts and types of foods offered. Complete freedom of choice is not implied, nor would it be practicable within the limits of the usual family's dietary.

Insulin is of course employed in all cases, usually a mixture of protamine zinc insulin and regular insulin given in a single dose each morning. The dosage is regulated to allow fairly continuous mild hyperglycaemia and glycosuria, but avoiding excessive glycosuria (which leads to polyuria and nocturia) and, particularly, with constant precautions to avoid acetonuria. The urine is tested usually three times daily, using the simplest tests available (Clinitest tablets for sugar and an acetone test powder); but after the routine is thoroughly established and conditions are fairly stabilized the frequency of testing is reduced, especially for the older children. The parents are cautioned that testing for acetone is most important when there are disturbances such as colds or other evidence of acute infections, diarrhoea, vomiting, headache, suddenly increased glycosuria, polyuria or nocturia, thirst, loss of weight, etc. The children also of course are taught

such principles as soon as they are old enough to assume even partially their self-regulation.

In the rationale of this plan of management a principal tenet is that the acute complications of diabetic acidosis and coma are never precipitated by »overeating» in the sense of overindulgence in carbohydrate (as is commonly claimed), but by careless omission of the usual dose of insulin or failure to increase the usual dose as needed during infections, even minor ones. This tenet is based on many clinical observations and on various metabolic studies such as those of MIRSKY and his co-workers, on diabetic children, and those of TOLSTOI, on adult diabetic subjects. These investigators and others have demonstrated that diabetic subjects can exhibit extreme degrees of glycosuria and high levels of blood sugar for long periods of time without developing acidosis if insulin is supplied in sufficient amount to promote hepatic glycogenesis and to avoid the production of ketone bodies. Therefore, for routine diabetic care under the glycosuric regime the appearance of acetone in the urine may be regarded as the best available practical indicator of the more serious metabolic derangements that occur when insulin dosage is too low.

Since 1942, when it was first tried in a few cases, the free-diet-glycosuric regime has been employed in caring for more than 50 diabetic children enrolled in this clinic. While this is a comparatively short experience, the results to date seem to support all the arguments in favor of this regime that are well summarized in Lichtenstein's papers. Ketonemic acidosis has occurred rarely, except in a few individuals who were careless and not amenable even to this liberal discipline. The average daily insulin requirements are practically the same as those observed among patients who previously for many years followed a stricter regime with measured diets. The average consumption of food is about the same as was usually prescribed for the measured diets, and about the same, with similar wide ranges of variation, as that of healthy non-diabetic children. Data demonstrating these points will be reported elsewhere later.

Summary

Diabetes mellitus occurred in three successive sibling infants, with onset of symptoms at 3 months of age in two and at 9 days of age in the third. The parents are non-diabetic but there is a history of diabetes in collateral branches of both families. The first infant died 14 hours after treatment with insulin was started, after having suffered severe acidosis probably more than 48 hours before the diabetes was recognized. In the other two, insulin therapy was started immediately when glycosuria was discovered. Both have been fed normal infants' diets, without restriction. The younger was breast fed 10 months on a »demand schedule», receiving 1 and 2 units of protamine zinc insulin daily. At $3\,^1/_2$ years and $1\,^3/_4$ years of age, respectively, both are receiving approximately 8 units of protamine zinc insulin and 6 units regular insulin daily, a dose that permits continuous mild glycosuria. They have never suffered acidosis, despite several intercurrent infections, and growth has been normal.

Résumé

Diabète sucré dans la première enfance, soigné sans régime alimentaire

Le diabète sucré se manifesta chez trois enfants successifs des mêmes parents, avec apparition de symptomes à l'âge de trois mois chez deux des enfants et de 9 jours chez le troisième. Les parents ne sont pas diabétiques, mais il y a une histoire de diabète dans des branches collatérales des deux côtés. Le premier enfant mourut 14 heures après que le traitement à l'insuline fut commencé, après avoir souffert d'une acidose grave probablement plus de 48 heures après que le diabète fut découvert. Chez les deux autres, le traitement à base d'insuline fut commencé dès que l'on découvrit la glycosurie. Tous deux furent nourris selon l'alimentation normale des enfants, sans restrictions. Le plus jeune fut nourri au sein pendant 10 mois, dans la mesure de son appétit, recevant 1 ou 2 unités d'insuline protamine-zinc. A 3 ans $^1/_2$ et 1 an $^3/_4$, respectivement, chacun recevait environ 8 unités d'insuline protamine-zinc, et régulièrement 6 unités d'insuline par jour, dose qui permet une glycosurie continue modérée.

Ils n'ont jamais souffert d'acidose, malgré plusieurs infections intercurrents, et la croissance a été normale.

Zusammenfassung

Diabetes mellitus im frühen Säuglingsalter, behandelt ohne diätische Einschränkungen

Bei drei aufeinander folgenden Kindern aus der gleichen Familie trat im Säuglingsalter Diabetes auf. Bei zweien von ihnen konnte man die Symptome im dritten Monat und bei dem dritten am neunten Tag feststellen. Die Eltern waren wohl keine Diabetiker, doch weiss man, dass in den Seitenlinien beider Familien es Fälle von Diabetes gegeben hat. Das erste Kind starb 14 Stunden nach Einsetzung der Insulinbehandlung, nachdem es schon 48 Stunden, ehe Diabetes erkannt worden war, an einer schweren Acidosis litt. Beim zweiten Säugling wurde sofort nachdem Glykosuria entdeckt worden war mit der Insulintherapie eingesetzt. Beide wurden normal ohne diätische Einschränkung ernährt. Das jüngere Kind erhielt 10 Monate hindurch die Brust nach einer gewissen festgelegten Einteilung und täglich 1—2 Einheiten Protaminzinkinsulin. Im Alter von $3\,^1/_2$ respektive $1\,^3/_4$ Jahren erhalten nun beide täglich regelmässig ungefähr 8 Einheiten Protaminzinkinsulin und 6 Einheiten gewöhnliches Insulin, eine Dosis die fortgesetzte leichte Glykosuria zulässt. Obwohl in der Zwischenzeit mehrere Infektionen konstatiert werden konnten, hatten die Kinder niemals Acidosis, und ihr Wachstum ist normal.

Sumario

Diabetes mellitus en lactantes tratados sin restricción dietetica

Diabetes mellitus se observo en tres lactantes, con iniciación de la sintomatologia a los tres meses de edad en dos de ellos y a la edad de nueve dias en el tercero. Los parientes no son diabeticos pero existe una historia de diabetes en las ramas colaterales de ambas familias. El primer niño murio a los 14 dias de iniciado el tratamiento con insulina, habiendo probablemente sufrido de una severa acidosis durante mas de 48 horas, antes de

haberse efectuado el diagnostico de diabetes. En los otros dos, la terapeutica con insulina fue iniciada al descubrirse la glicosuria. Ambos habian sido alimentados con dietas de niños normales y sin restricciones. El menor fue alimentado a pecho durante 10 meses segun un esquema de demanda, recibiendo de 1 a 2 unidades diarias de protamina-zinc-insulina; a la edad de tre años y medio, y uno y tres cuartos respectivamente, ambos reciben aproximademente 8 unidades de insulina-zinc-protamina y 6 unidades de insulina normal por dia, dosis que permite una leve y continua glicosuria.

Nunca han tenido acidosis, a pesar de varias infecciones intercurrentes y el crecimiento ha sido normal.

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Dementia Infantilis Heller

by

SIV GUNNARSON

In 1908 HELLER published six cases with a clinical picture of what he called dementia infantilis. By the year 1930 he had collected twenty eight cases with the same symptoms. Still more cases have been published by WEYGANDT, ZAPPERT, and MONTESANO. Altogether some fifty cases have been described.

The disease begins at the age of three—four years among children who earlier were quite normally developed both physically and mentally. The children become restless and agitated and manifest speech disturbances. Words which they could previously say become fragmentary, echolalia develops, and the articulation is impaired. After some months these children are very demented, while the facial expression remains intelligent. They reveal instinctive love of destruction and display emotional outbreaks and states of fear and anxiety, with occasional apparent hallucinations. The speech impairments gradually lead to a complete loss of the faculty of speech. Unlike children with dementia praecoxissima, these are not autistic but remain affectively accessible to some extent.

There has been much discussion as to whether there really is a question of a special clinical picture or only an early exhibition of schizophrenia. LUTZ (1938) is of the opinion that the aetiologic connection cannot be looked upon as elucidated, due to the fact that little is yet known relative to the cerebral, anatomic changes. KANNER (1942) states that the majority of authors nowadays agree that dementia infantilis is a special disease and not an early

form of schizophrenia. TRAMER, 1942, while holding the same view, is convinced that there is an endogenous degenerative process in the brain — accordingly, a heredo-degenerative disease in childhood years. Pathologico-anatomic descriptions have been given of fatty dough-like states of cerebral tissue like those in amaurotic idiocy, but in other cases this condition is missing.

In the past year we have had a patient under observation at our hospital who manifested a picture which we interpreted as dementia infantilis HELLER. Because of the rarity of the clinical picture we consider it worthy of report.

The patient was a girl, five years and four months old on admission, the second child of a family in good social circumstances. Heredity: the maternal grandmother was nervous and quarrelsome and the grandmother's two cousins were insane. The grandfather was a habitual drunkard. Both parents were healthy, but the mother had more recently been nervous. Delivery had been normal; the child's weight at birth was 3 290. Her condition after birth was good. She took naturally to the breast and developed normally. She could sit up when she was six—seven months old, appeared fully normal as an infant, and walked when she was thirteen months old. She smiled and grasped at things at the ordinary time. She spoke odd words, such as »papa» and »mamma», as early as eight—ten months, certainly at twelve months.

At the age of two and a half she was bright and normally developed. She then began to sleep badly, screamed and jumped up in the night, and was difficult to calm. When the patient became agitated every means was tried to calm her, first kindness and then whipping, but nothing helped. She would alternately drink and urinate. Almost simultaneously the child began to manifest agitation in the daytime. When she was two years and nine months old she was taken to the outpatient department of a children's hospital and was given phenemal tablets. On this occasion she was tested and found to have an intelligence quotient of 59 according to BÜHLER-HETZER. At the age of three she still spoke isolated words and the parents began to feel troubled. Since then she has become more and more motionally agitated.

She refuses to wear knickers, stockings, or shoes. She still wets the bed but since the age of two and a half she has been dry during the day. She spits at people, both childern and adults, and cannot play with other children, whom she is unable to contact. She is fond of swinging but can scarcely play at anything else. The child's condition has become steadily worse from the time agitation began at the age of two—three. The parents have disagreed to some extent about her upbringing. Both are hot tempered and there has been a good deal of contention. The child has been slapped or spanked with a cane rather often, and she is apparently afraid of punishment. If she knocked a glass of milk over on the table or broke any china, she was whipped.

The mother is a schizoid type. She betrays no feeling for the child and is uncertain and unhappy. The father says that she has never been able to manifest spontaneous compliance or warmth or behave naturally towards the child. The father is more frank and accessible and seems to be in more normal contact with his fellow men.

Investigation revealed the following. The patient was of normal length, somewhat thin, and in view of her behaviour and intellectual capacity had a tense and strikingly alert and bright facial expression.

A physical and neurologic examination disclosed nothing in particular. Refl. normal. W.R. neg.

It was the patient's habit to enter a room like a little whirlwind, and immediately throw herself into the arms of persons she had never seen before. She climbed up on their knees, stroked and fondled them, fingered their throats and hair and in every way sought after physical contact. She was much motionally agitated and restless. Upon catching sight of Miss E., with whom she had had contact earlier, she shouted her name in baby language and rushed over to her, scrambled up on her knees, and fingered her hair in the manner described above. She made small ape-like gestures with the hands. Behind the affected exhibitions, no feeling could be traced. Her behaviour was theatrical and like that of a marionette. She snapped up names and simple words and repeated them over and over again. She continued for a long

time to interchange the names of the doctor and nurse, turning her head from one to the other. She obeyed such simple orders as to greet persons, in doing which she curtseyed theatrically and with extreme politeness. She was very diffusive, flying from the one to the other, and was unable to concentrate for more than a minute. If one played with her, for instance, with coloured rings on sticks, is was possible to capture her attention only for a minute or two. She threaded the rings willingly but in a stereotyped manner and lacked the sense to assort them according to colour. If questioned as to the colour, she gave the correct answer with obvious pleasure. Many intonations and expressions appeared studied, as did the gestures. In spite of all these clinging exhibitions one had no contact with the child. She was like an empty shell. She spoke incoherently, using only disconnected words, staccato and ejaculatory. She sought continually to attract attention towards herself. She was unable to amuse herself. The nurse in her section likened her to a little trained animal and this picture is remarkably to the point. Her I.Q. according to Terman was 49.

In the ward she flew from one thing to the other in motional agitation. She had to be watched continually when she was up. She could never be set to do anything and took every opportunity to break or destroy everything she came across. In one unguarded moment she intentionally upset a whole bedside table. She was always delighted after such events when fragments whirled and there was commotion.

She had no contact with other children, but when an adult entered the room, even a stranger, she climbed up on him and settled down for a minute or two with her arms round his neck. The disconnected words she shouted were always an echo of what she had snapped up around her.

To sum up, it can be said that the symptoms of this patient coincided with the picture of dementia infantilis HELLER. In the beginning normally developed, she became acutely ill later, the chief symptoms being motional restlessness, emotional outbreaks, agitation, speech disturbance, and echolalia. Increasing dementia dominated the picture, with a relatively alert facial ex-

pression retained. The only deviation from cases earlier described is that the symptoms appeared as early as the age of two and a half years. In most of HELLER's cases and those published by other authors, the symptoms did not become manifest before the children were three—four years old.

With regard to differential diagnosis, one must first consider imbecility and dementia praecoxissima. Against imbecility is the question of judging the value of the parents' information that in the beginning the child was normally developed. Such statements must obviously be regarded with scepticism, but the fact that the child sat up at seven months and walked at thirteen argues in favour of their correctness. It seems scarcely probable that an imbecile child with an I.Q. of 49 could be so motionally developed at such an early age, and this same early development also favours the accuracy of the parent's statements.

Dementia praecoxissima is indicated especially by autism, which in this child was missing. Although manifesting no deeper contact with her surroundings, she was the opposite of autistic in her perpetual fluttering about and contact-seeking.

Thus the indications for the most part point to a presumably early development of dementia infantilis HELLER.

With regard to therapy, the question is where to place such a child? Unfortunately this is far from easy. We lack a department where a psychotic child can be under observation for a longer time. For such cases, there is only one private institution and an institute for imbeciles to choose between. The former place is unable to receive patients at present, and the latter is out of the question. It is extremely regrettable that the community has so few ways of taking charge of such a child. On the one hand, it is very difficult to tend a patient when the parents are at the point of breaking down, and the mental state of healthy children in the home is severely threatened by the anxiety which is created. On the other hand, a prolonged observation of such an uncommon clinical picture is exceedingly desirable. If the diagnosis is correct, the prognosis would be infaust with progressive dementia.

Summary

A description of HELLER's infantile dementia is given and the case of a girl seen at the age of five years and four months is presented. Her symptoms started earlier than usual, at the age of two and a half years. The differential diagnosis is discussed and the difficulty of finding institutional care for such patients is pointed out.

Résumé

On décrit la démence infantile de HELLER, puis on aborde le cas d'une petite fille de 5 ans et 4 mois. Ses symptômes commencèrent plus tôt que d'habitude, dès l'âge de 2 ans et demie. On discute le diagnostic différentiel ainsi que la difficulté d'hospitaliser la patiente dans un établissement approprié.

Zusammenfassung

Gegeben wird eine Beschreibung von HELLERS infantiler Demenz und der Fall einer Patientin im Alter von 5 Jahren und 4 Monaten. Ihre Symptome begannen früher als gewöhnlich, nämlich im Alter von $2\,^1/_2$ Jahren. Die Differentialdiagnose wird erörtert. Die Schwierigkeit, eine Heimpflege für derartige Patienten zu finden, wird dargelegt.

Sumario

Se da una descripción de la demencia de HELLER y se presenta el caso de una muchacha de 5 años y 4 meses de edad. Los síntomas de esta muchacha empezaron más pronto de lo natural, a los $2\,^1/_2$ años. Se discute la diagnosis diferencial y se recalca la dificultad de disponer servicio facultativo para esta clase de enfermos.

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General BCG Vaccination of the Newborn as Safeguard Against Tuberculosis During Infancy

by

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There has been a very satisfactory and steady decrease in the TB mortality rate in Sweden for at least the last thirty years. In 1915 the mortality figure for the entire country was 2.03 ‰, for Stockholm 2.73 ‰, as against only 0.59 ‰ and 0.66 ‰ in 1945 (see BERG 1948). Nevertheless, the mortality rate of this disease is still (1945) the fourth highest in the country; and if positive tuberculin reactions are any proof, then practically every town-dweller, at least, has had a tubercular infection before the age of forty—fifty years, with or without clinical symptoms of the disease (WALLGREN 1947 a). The need of some safeguard against TB is therefore still very great.

In a civilized community, where constant contact with others is unavoidable, it would seem that successful active inoculation would best protect the population against dangerous and fairly common maladies the sources of infection of which can only with difficulty be kept down with adequate certainty. The less effective the medical treatment available for such diseases, the more the need of inoculation increases. In Sweden, TB indisputably falls within this category. The active inoculation which the BCG vaccine provides is therefore a very valuable weapon. It has won great confidence in Scandinavia, and its use in Sweden of recent years has been more and more widespread. WALLGREN (1947 b) estimates that in 1945 about 200 000 persons were inoculated, most of them for the first time. The intracutaneous method of inoculation, which in Sweden has been recommended and tested

by WALLGREN (see, e.g., WALLGREN 1947 a), was far and away the most popular in this connection.

Hitherto it has been assumed (WALLGREN 1947 a) or accepted (WALLGREN 1947 c) that no immunity is obtained during the incubation period of the BCG vaccine, the end of this period being set at the point when the subject reacts positively to at least 1 mg Mantoux. This view presupposes immunity from the vaccine only when the said reaction is produced *before* the subject encounters infection. Hence the imperative need which Swedish physicians postulate of isolating the inoculated subject — at least for the whole of infancy, though naturally the principle holds for all ages, if possible — from persons suspected of being infectious until he responds positively to the tuberculin. The results of LEVINE and SACKETT (1946) are considered to show that this precaution is still neglected, resulting in no protection to the subject.

The question of preventing the contraction of TB by BCG vaccination, and with it the question of thus vaccinating all newborn children as a safeguard in infancy, turns, therefore, on the possibility of avoiding infection during the unsafeguarded period mentioned above.

There is no doubt that even — indeed, particularly — in early infancy, susceptibility is great and some safeguard desirable. Infant TB has a considerable mortality rate. A survey by SÖDERLING (1939) shows a rate of 60 %—70 % during the first year of life, and JORUP (1946) has a similar figure of 60 % for the first three months of life.[1] JORUP's material includes TB cases aged one day—two years from children's hospitals in Stockholm during the years 1940—1944. It comprises two hundred and one cases, with thirty nine deaths. Thirteen of the children were less than three months old when they fell ill, and of these eight (60 %) died. We are not told how many fell ill during the first and second half years of life, respectively. JORUP's article ends by demanding Calmette vaccination of all infants. The most suitable point for this would without doubt be before the child leaves the

[1] In a later work (JORUP 1948; see below) the death rate during the first half-year of life was 80 %.

maternity ward; in view of the newborn infant's less good powers of reaction, however, it may well be that it would be better to vaccinate at some later point during the first three months of life, on the strict proviso that it can be taken more or less for granted that the child will not be exposed to tubercular infection in its home. LIND (1947) takes JORUP's results to show that there is everything in favour of the child's being inoculated at the maternity hospital, if possible.[1]

If, as hitherto supposed, it is true that there is no immunity before a positive reaction sets in, it follows that the children must not be exposed to infection until the inoculation has produced this response. They must therefore be isolated from sources of infection until this has taken place.

It was previously supposed that it takes six—eight weeks after inoculation before the subject has a positive reaction; this can be adduced from the present regulation that the result of BCG inoculation must be reported *at latest* two months after it was performed (M.F. ser. A 95/1943). Recently, however, it has been found that infants inoculated at birth often do not have a positive reaction until three or even four months later. TÖRNELL (1947), for example, obtained a scant 50 % of positive reactions from infants inoculated at birth when 'reading off BCG after about six weeks'. He therefore considers it 'may be advisable on practical grounds to postpone reading off such results till the third or fourth month. About 98 % will then show a positive reaction.' This latter juncture is important, but needs narrowing

[1] In a survey (JORUP, November 1948) published after the present article was written, JORUP treats TB cases up to and including fourteen years of age treated at Stockholm children's hospitals from 1945 through the first half of 1948. One hundred ten children aged one day—two years were treated. A diagram indicates that forty three of these fell ill during the first year of life and sixty seven during the second. Ten of the former and two of the latter died. He says there were more deaths among those falling ill during the first three months, but does not give the number. JORUP reports further that all except one who fell ill during the first half year of life succumbed to familial, often newly discovered infection, and stresses 'the extreme importance of BCG vaccination of preferably all children before they leave the maternity hospital, by which means most cases of infant TB could undoubtedly be avoided'.

down. It allows a range of seven to sixteen weeks after vaccination for the registering of results. The first, i.e. seven weeks, is more or less the one formerly used, and as TÖRNELL was setting out to show that in 50 % of all cases a positive reaction is set up considerably later than can be obtained in the time now adopted, he has been taken to mean that the high percentage of such responses is obtained when the results are read off about twelve—sixteen weeks after inoculation. As regards infection, then, it is the whole of this time which might be, and often is, unsafeguarded. Again, as regards the possibility of contracting TB despite apparently successful inoculation at birth, this unsafeguarded period must be extended by the incubation period (i.e. at least four—six weeks) for an infection contracted at the last possible moment before a positive reaction appears. This makes a possible total of five and one half unsafeguarded months. Clearly, then, even in the most favourable cases BCG vaccination of the newborn cannot guarantee *any* child against TB during the first three months of life — nor, if TÖRNELL's figures are to be taken as the norm, more than at most *half* of the children even during virtually the whole of the first half year of life — not, that is to say, unless they are effectively isolated from infection until they react positively. If this condition is not fulfilled, inoculation at birth can safeguard against TB only at ages after the above-mentioned, and even then only if the inoculation takes and the child is infected after this juncture and while it is still reacting positively to tuberculin. Nevertheless, quite a number inoculated at birth never respond even to 1 mg Mantoux, however perfect the technique used in inoculation and testing. Thus a calculation of LIND's values (1947), obtained in Stockholm from concurrent tests with 1 mg Mantoux and plaster and ointment seven—ten weeks after giving newborn infants 0.05 mg of the vaccine, shows 20 % (sixteen children of seventy eight) negative to 1 mg Mantoux, and another 20 % (twenty five of one hundred and thirty one) negative on inoculation with the double dose, i.e. 0.10 mg. The latter result is interesting because it shows that the frequency of the reaction to 1 mg Mantoux did not increase when twice as much vaccine was given. If the inoculation was considered to have

taken if either the Mantoux or the plaster and ointment test was positive, this would give respectively 86.5 % and 95.3 % positive reactions. As the total percentage of positive reactions is higher than that for 1 mg Mantoux, made at the same time with the percutaneous method also, this must mean that the former percentage includes a number of so-called positive inoculations which were tested only by percutaneous methods, or which reacted positively to these and negatively to 1 mg Mantoux. Acceptance of the higher percentage admits that children may react positively to percutaneous tests but negatively to Mantoux, and may even so have obtained protection from TB. This is an interesting question, particularly as subjects have sometimes been found more sensitive to percutaneous tests than to Mantoux; it does not, however, tie up on the one hand with the fact that physicians have been unwilling to rely on a positive reaction confined to percutaneous tests and on restricting themselves solely to such tests, and on the other with the fact that Mantoux up to 1 mg is recommended direct, without previous percutaneous test, to establish that the inoculation has taken. Be this as it may, as long as this opinion holds it looks as though the practical standards for LIND's percentages must be dictated by the number of positive reactions to 1 mg Mantoux (80 %) which were obtained in tests both with Mantoux and percutaneously on one and the same child. In another investigation (GYLLENSWÄRD 1949) from a different part of Sweden covering the years 1940—1947, only about 50 % of the cases were reported as positive after a first inoculation. This was performed in clinics, in most cases during the neonatal period, though some were done later, during the first year of life, with a dose of 0.05 mg vaccine. Percutaneous tests were made first and followed up with 1 mg Mantoux when the reactions were negative. Another half of those reacting negatively to this latter test became positive after a fresh inoculation. In all, then, three fourths of these cases reacted positively to some test after two inoculations in the first three months of life. The results were read off very regularly and meticulously at fixed times (for Mantoux, every seventy two hours, and a reaction of at least 10×10 mm was required). Other investigations have sometimes yielded higher

positive percentages, but these may have been influenced by different principles of registration, and some irregularity in following them. The important result is the one that presents itself as a general rule. It must therefore be assumed that at least every fifth child (LIND 1947), and perhaps every other (GYLLENSWÄRD 1949) might lack protection even if every one were inoculated at birth with BCG as a matter of routine. Now, one means of combatting TB is to isolate the newborn infants known to be threatened with the disease until the vaccination has taken. The children not known to be so threatened are not isolated, so that if they are to enjoy the relative security of the first category, and indeed if the battle against TB is to be waged with still more success, it is obviously essential that the results of the inoculation be controlled, and that the subjects be reinoculated when necessary. This principle also holds for BCG vaccination at other ages, even though the percentage of positive reactions seems to be higher there.

There is another hard and fast rule that must be followed if BCG vaccination of the newborn is to ward off TB either during approximately the first six months of life or, when a first vaccination is negative, at all subsequent ages until six or possibly more weeks have elapsed after a fresh inoculation has taken. This rule is that one should know whether there is any risk of infection during the time a positive reaction takes to develop, the point being that only infants growing up in surroundings where the TB menace is known to exist can be isolated and regularly reinoculated when necessary.

This necessity comes out best if we weigh the chances of using BCG vaccination to safeguard the group which, in JORUP's cited investigation, strikes us as most tragic by virtue of its high mortality rate — namely, the children who fall ill during the first three months of life. We have said that children are not isolated when no TB menace is known to exist, and that the earliest date for immunity (positive reaction to tuberculin) is, under all conditions, six weeks after inoculation during the neonatal period; this being so, then both these children and — according to TÖRNELL's figures — at least every other of those who become in-

fected during the first three months or so of life, but who fall ill during the second or even the third three months, are unsafeguarded during the actual period of infection, even if they have been injected with BCG vaccine and the inoculation has been successful as such. These children would run the same risk of falling ill and dying as if they had not been inoculated at all, so that BCG vaccination of all newborn subjects is not, by itself, enough.

Hitherto, little regard seems to have been paid to the possible danger in our country of the child's unwittingly coming up against TB before a positive reaction has followed inoculation at birth. Or perhaps the present tuberculosis control seems to minimize this risk; otherwise, it would hardly have been so unreservedly proposed that infant TB can be kept in check by general BCG vaccination of the newborn. An inspection of the sources of infection in JORUP's material brings home very strongly, however, both how great a part these elements play and the risks to the children that they involve. The fact is that nearly 30 % of all the cases in this material had been infected by an unknown source — the same figure, incidentally, as in SÖDERLING's earlier material of cases aged six months to two years — and there was a further 40 % of newly discovered cases of TB, with an additional 30 % infected by TB subjects under observation. Nearly three fourths of the sources of infection, that is to say, were not known to the Clinic authorities. The remaining known cases had not troubled to follow the prescribed precautions for preventing the spread of infection, or else had been considered non-infectious.

According to this investigation, then — and it concerns no less a center than Stockholm — the children contracting TB in the two first years of life were, virtually without exception, not known to have been threatened with infection, and were therefore neither BCG-vaccinated nor isolated. This risk is of great importance in determining the value of BCG vaccination before any inoculative protection has had time to form, however young the subject may have been. On the other hand the number of cases in which vaccination was not performed in spite of a known threat

from TB is very small, though the incidence of the disease in these cases is shocking enough.[1]

The idea that there is a considerable risk of infection that cannot be controlled has been greatly reinforced by a recently published investigation by GENTZ and BLUHM (September 1948) into the frequency of active TB — which had nevertheless escaped the control of the authorities — in women just become mothers, an intensive check-up of welfare centers and maternity hospitals in Stockholm during the years 1944—47 having revealed respectively twelve, eighteen, eleven, and eleven thitherto unknown cases of 'unmistakably active TB' in such women. The true significance of these figures only comes out, however, if they are compared with previously known cases in the same category — known, that is to say, from what we shall have to call routine checking-up at a dispensary. These latter figures were four, thirteen, five, and four, respectively, i.e. only twenty six previously known cases as against a total of fifty two newly discovered ones. A comparison between the number of investigated mothers and the birth figures for Stockholm seems to show that about four fifths of the total number came under observation. It may therefore be necessary to allow for even higher figures than the above for active TB cases among women recently giving birth. Thus if the intensive check-up mentioned above had not been made, only one third at most of all cases, even in the most threatened group — i.e. children of mothers with unmistakably active pulmonary TB — could have been isolated during the most precarious period following a BCG vaccination. There is hardly any reason to suppose that this group was smaller before 1944—47 — rather the contrary, since the frequency of TB in Sweden is on the decline. It is true that the absolute figures are small, but we are concerned here with the general risk of infection by TB at an early age, and growing out of this the possibility of universal BCG vaccination of the newborn as a means of saving a number of children over

[1] In JORUP's survey (1948) for the years 1945—47 and the first half of 1948, the distribution into groups of the sources of infection is almost exactly the same, even though ages up to and including fourteen years have now been included.

and above those who are protected by the less extensive vaccination of children known to be threatened by TB. JORUP's figures alone show that this number is not large, particularly when compared (though this comparison does not give quite a true picture) with the number of living children born in Stockholm during the years 1940—1944, i.e. 55 500. The risk of contracting TB during the two first years of life taken as one unit would be about 3.6 per thousand, and the mortality risk 0.7 per thousand. An example of how the risk of infection has been assessed is given by GENTZ and BLUHM's material of four thousand eight hundred and ninety eight children, including those of the tubercular mothers discovered during the check-up, who were BCG-vaccinated at birth in Stockholm in 1947, and among whom only eighty two were considered to need isolating (and probably a number of cases protected by removing the source of infection).

But the relatively, if not numerically, large group of children the active TB of whose mothers had not previously been known must, as far as one can see, be supplemented by another at least as large. GENTZ and BLUHM say that the intensive check-up was carried out only on the female parent. It is highly likely that if it had been extended to the fathers, it would have revealed at least as many — and, as we shall soon see, probably more — cases of previously unknown TB of the same character among them. Added to these are the various inmates of the homes, relations and others — certainly a by no means negligible category in view of the present housing shortage, in Stockholm in particular.

Further support for the existence of this larger risk group can be found in the home conditions of the BCG-vaccinated children dealt with in my recent survey (GYLLENSWÄRD 1949; see above). The material came from a home for children in Uppsala, and consequently came under a different TB clinic. Among one hundred and eight children injected with BCG and isolated from their homes during the years 1940—47, TB of the mother alone dictated the need for isolation fifteen times more often than TB of the father alone. It is true that this proportion does not, as it stands, show the distribution of the known TB threat among mothers and fathers: 25 % of the mothers were unmarried, and

these do not very often, or even as a rule, live under the same roof as the fathers. In such cases, possible TB in the fathers is not a reason for admitting the child to a home. Moreover, isolation from a tubercular mother with probably infectious TB usually means that the child must be sent away, whereas it may be possible to keep a child from a tubercular father without sending it to a children's home. This, however, is very difficult to arrange in the social group III, i.e. the lowest social group in the country, which is the one in question here, unless the father is sent to a tuberculosis sanatorium — a solution which was sought, and which often seemed to succeed. It has not as yet been possible to make any report on it, however. But even taking these circumstances into account, the difference in TB frequency is so remarkable as to indicate quite clearly how much easier it has been to investigate the mothers than the fathers. It is therefore interesting to see whether any other light can be thrown on this question. GENTZ and BLUHM give their reasons as to why the clinic authorities have not previously been able to run to earth the, relatively speaking, highly important group of TB cases who constitute the greatest danger to the newborn children, i.e. those represented by mothers with TB. In their opinion, the mothers quite simply evaded control, either because they did not come to the welfare centers, or if they did that and were told to report to the photo-fluoroscope department, they failed to do the latter. There is no way of getting into touch with the fathers corresponding to the mothers' welfare centers, and consequently less chance of getting them to submit to the kind of control exerted there. JORUP's material gives no direct information on this point, but some can be gathered indirectly from the statement that when it could be pinned down, the source of infection was found to be the father in forty eight cases, as against only thirty two where it was the mother. The difference seems too large to be ascribed to chance. Indeed, if no precautions had been taken, it might have been expected to have been rather the other way round. These precautions must, of course, in the first place consist of the isolation of the children of tubercular parents from the source of infection. In that case, the only other plausible reason for the

difference must surely be that the TB of the fathers is less often known about than that of the mothers, particularly when — as pointed out above — it should be easier to isolate a child from its father than from its mother, and the risk of infection from the latter is, other things being equal, usually considered to be greater.

There is hardly any reason to suppose that the results obtained by GENTZ and BLUHM and by JORUP are inapplicable to the whole of Sweden. On the contrary, they should bear on problems of at least the same size in other parts of the country, since the TB frequency there is generally about the same as in Stockholm and, in many places, higher, while the average chances of tracking down tubercular subjects must be considered to be lower than in the capital.

The chances whether these unknown sources of infection do or do not overtake the inoculated subject during the vaccine's incubation period must be said to be very difficult, if not impossible, to assess. The same is true of the risk run by a subject where the vaccination has not taken. It is precisely this elusive danger of infection that brings home the need of inoculative protection with particular force. But this would not justify the belief that children, and particularly those in early infancy, would be safeguarded against TB merely by the institution of a BCG vaccination of all newborn infants. The infection has been shown to be thoroughly incalculable, and often to be present unawares in the mothers and/or the fathers and other inmates of the home; the lamentable conclusion must therefore be that, unless some protection has developed before a positive reaction to at least 1 mg Mantoux has set in, a measure consisting solely in the extension of the BCG vaccination to cover all newborn infants would not be very much more efficacious than BCG vaccination of just those children known to be under the shadow of TB — not, that is to say, if the aim is to combat TB during the first three months of life and, largely speaking, during the entire first half year. Furthermore if, as obviously can happen, the percentage of positive reactions is often relatively low or at any rate dubious, the value of such an inoculation in preventing children over six

months old from contracting TB during that period when the reaction would still have been positive if the inoculation had taken, would be correspondingly limited. It might even happen that BCG vaccination at a rather greater age would produce as speedy a safeguard, give a stronger and more durable defense, and protect more children than would an inoculation of newborn infants. If, that is to say, it takes longer to obtain a positive reaction to tuberculin in the neonatal period than rather later, then an inoculation performed as much later as the time needed for development of positivity was shorter would yield protection just as early, and, if the percentage of positive reactions in the latter case is greater, would protect a correspondingly larger number of children. Finally, if the positive reaction is stronger, then both the strength of the protection and its duration would presumably be correspondingly better.

Now it is interesting to point out that on the above-mentioned, hitherto generally accepted premises, a BCG vaccination of all newborn infants would not have saved a single one of JORUP's thirteen children who fell ill, and eight who died, during the first three months of life. Plainly, all of them must have been infected before a positive reaction had time to set in, and the apparently necessary measure of isolating them from the source of infection until this had occurred neither would nor could have been taken, since the risk was unknown. These children alone constitute one fourth of all those who died after contracting TB during the two first years of life. For reasons just given we must add those who were infected during the first three months of life before the vaccine had time to set up any protection at all, or fell ill, though not until the second and possibly even the third three months of life, following a negative reaction. The number of these children cannot be elicited from JORUP's figures.[1]

[1] Nor would BCG vaccination of newborn infants have protected the children contracting and dying of TB during approximately the first half year of life which JORUP handles in an amplifying survey (1948) mentioned in a previous note. On the contrary, this survey bears out what has been said. It covers the years 1945—47 and the first half of 1948. A diagram shows that probably forty three children fell ill, and ten of them died during

The degree of protection enjoyed by the other children in JORUP's survey would depend on how far the inoculations took, and whether this occurred before the occasion of infection.

All this unfortunately goes to show how rash it is to hope too much from BCG vaccination of preferably all children while still in the maternity wards, and how uncertain it is that this is the best way to avoid most of the cases of infant TB, at least as regards deaths. It must, rather, be acknowledged that an inoculation of all newborn infants would leave a considerable number of children as unprotected as if nothing had been done. The advantage of inoculating all children instead of only such as are exposed to a known TB risk would be that, while the vaccine was still effective, protection would be provided for some of those children who now contract TB at any time *after* the first three months of life. But this would apply only to such children as are tuberculin positive, and who have time to become so before they are infected, and who, moreover, would have been inoculated either not at all or too late if only children known to be threatened by TB had been given the vaccine. However, as has just been said, it is not categorically established that the best effect in this direction is obtained by concentrating on the newborn.

A further not entirely negligible point is that the wider use of inoculation may also, to some extent, increase the risk of infection. A percentage of inoculations which, in some surveys at any rate, may be considerable does not seem to lead to tuberculin

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the first year of life. JORUP does not say how many fell ill and how many died during the first three months of life, but he states that deaths were most frequent among those who fell ill during this period. The mortality rate during the second half year was only 8.6 %, as against 80 % in the first half year. In view of this, and allowing for the fact that JORUP's eight deaths during the first three months of life referred to a five-year period (1940—44) as against the three and one half years of the present survey, where there were ten deaths during the first year of life, the number of deaths during the first three months of life hardly seems to have fallen. Nevertheless, the frequency of BCG vaccination among the newborn had risen very greatly. According to JORUP, at least one thousand newborn infants were vaccinated at the Maternity Hospital in 1945, about three thousand in 1946, and about six thousand in 1947.

positivity. The danger may then be that an inoculation where the subsequent reaction is not checked on may be assumed by the public to have given protection as a matter of course. It is possible that inoculated children who have not taken, though their parents think they have, may be exposed to tubercular contacts which would otherwise have been carefully avoided.

Summing up, then, it must be said that even inoculation of all newborn infants cannot with certainty safeguard *any* of the children who may fall ill during the first three months of life, nor perhaps *half* of those succumbing during the second three months; nor yet any children, nor matter what their age, whose inoculation has failed to take. To ensure protection for these children the vaccination, whether made during the neonatal period or at some later, more convenient, juncture, must be combined with an intensified TB check-up, not only of all the mothers but also of the fathers, the inmates of the homes, and possible contacts as a whole. This applies particularly to those children falling ill in early infancy, since in such cases the infection practically always comes from some member of the family (see JORUP's investigation). Such a measure must therefore be regarded as more important than a mere BCG vaccination of the newborn; and it is imperative that it should be taken to combat TB during approximately the first half year of life, since only thus can the vaccinated subjects be isolated from sources of infection until such time as the vaccination has finally become effective. GENTZ and BLUHM stress the desirability, not to say the necessity, of this kind of intensified control of the mothers. This, however, is not enough; as already mentioned, a check must be kept on the fathers and other inmates of the homes. Furthermore, it is plain that such control is necessary for the sake of other mothers and their children in cases where, as is already very usual and seems to be getting even more so, delivery takes place at a public institution, which makes the risk of infection with TB considerably greater than has hitherto been assumed. This danger is emphasized by GENTZ's figures for mothers in Stockholm at the beginning of the 1940's: he found 44.2 % to be tuberculin negative in the age-group fifteen—twenty years and 38.6 % similarly negative in the

group twenty—twenty five years. Furthermore, the reaction should be checked as soon as possible, in order to avoid loss of time and therewith a prolongation of the unprotected period if reinoculation should prove necessary.

The facts adduced above do not, unfortunately, leave much room to hope that a more general BCG vaccination of the newborn would prevent TB during the first half year of life much, if at all, more than is achieved by the inoculation of children known to have TB contacts; indeed, it would seem to be quite useless in view of the obvious and frequently proved fact (cf. JORUP, above) that the infection during the first half year of life nearly always comes from some member of the family. The results of LEVINE and SACKETT are therefore in no way surprising, while at the same time they help to confirm the views put forward above. Inevitably few, also, are the chances of carrying out the other measure indispensable if children at this age are to be protected, i.e. intensive investigation of the home milieu to track down any possible tubercular elements. For large parts of the country, such investigation of the mothers alone must well be a counsel of perfection for a long time to come. And even if the mothers could be examined, there is still the risk from fathers and other inmates of the home, as well as other contacts that have proved even more difficult to cope with. Nor are the prospects rosy even for the third, obviously necessary measure, i.e. a far more effective isolation from known TB risks than is at present in force. After all, between 25 % and 30 % of all cases in JORUP's material were infected from known sources, several of which had not been considered by the clinic authorities to constitute any danger. And, if the percentage of positive reactions is low and the resulting protection of short duration, vaccination cannot be expected to be much use in safeguarding children at ages over about six months, either.

Under these circumstances, it is all the more surprising to see how remarkably seldom BCG-vaccinated infants actually do contract TB and die; this is most marked in the first half year of life, but also applies to infancy and early childhood. Even during the neonatal period, but also after this, it is difficult if

not impossible to control the relatively great danger of infection during the vaccine's incubation period. On the other hand, BCG vaccination is nowadays very widely practised in Sweden. In 1947, for example, half of all the children born in Stockholm were inoculated before they were a week old. BCG-vaccinated children might therefore be expected to be relatively common among those contracting TB very early in life, and also to be plentiful among TB cases generally. Surprisingly enough, however, neither of these things seems to be the case. This makes us look with some attention at JORUP's BCG-vaccinated children who contracted TB despite the inoculation. However, there are only three such cases in a total of two hundred and one. One was a child who was given the vaccine at birth and was then in a children's home for some considerable period; not until the age of twenty months did it contract a possibly tubercular complaint from which it subsequently recovered. The second child was inoculated when it was fourteen days old and died of miliary tuberculosis, thought to be a uterine infection, at the age of seven weeks; it was not known to have been exposed to TB sources after birth. The third case was vaccinated at an Outpatient Dep't. at the age of four months. At that time it was already living in the same room with a father mortally ill with cavernous phthisis, and was subsequently admitted 'not one year old' to a children's hospital; here it was found to be Moro-positive and possibly suffering from TB, but afterwards got well. This was the only case JORUP considered to have been infected with TB 'before immunity from the vaccination with BCG had developed' — if, that is to say, the child had TB at all. Both possibilities are open to discussion. In point of fact, however, what is surprising here is the complete — with the possible exception of one or at most two cases — absence of TB cases infected during the incubation period of the vaccine. And this impression is strengthened if we look at the large number of unknown sources of infection which could exist at the time of vaccination, some of which sources are shown directly, and others suggested, in the results of GENTZ and BLUHM; nor could the children have been isolated from them during the critical period, i.e. two and often perhaps three—four

months while the vaccine was taking and the entire period of observation in cases where no positive reaction was obtained. BCG vaccination and infection during the incubation of the vaccine would have been a perfectly possible combination, since a considerable number of such vaccinations were performed in Stockholm on children under two years during at least some of the years in question. According to GENTZ and BLUHM, for example, at least one thousand one hundred and seventy four children among the newborn alone were thus vaccinated in Stockholm in 1944.[1]

It is conceivable that infection was not passed on by the thitherto unknown group of sources (a large number of mothers with active TB), but this possibility cannot be reconciled with GENTZ and BLUHM's claim that — admittedly not in 1944, but in the following year — they found the intensified check-up by the clinic resulting in a decrease of as much as roughly one third in the number of infants contracting TB; this they ascribe to the fact that even the newborn in the newly discovered group were isolated from their mothers — the sources of infection — until the BCG vaccine had taken effect. If this is correct, it presupposes that the group of children who were inoculated without being known to be threatened by TB did not happen to include any of those in the above-mentioned group, where the risk of TB was undetected but nonetheless present. For if children in this latter group had been inoculated early, they must have been infected before the vaccine took effect if the new measure, i.e. isolation, was to have served its purpose. In this case, JORUP's material should contain quite a number of children who were BCG-

[1] In the three following years, more than one thousand, three thousand, and six thousand children, respectively, were vaccinated with BCG (see above). JORUP's later survey (1948), totalling six hundred and seventy one under fourteen, contained only twenty three who had ever been given the vaccine. Seven were considered free from TB, which leaves sixteen — an astonishingly low number. Of these, five showed signs (though these were not certain in all cases) of TB, although the effect of the vaccine should not at the time have worn of. There are then eleven children left. Their ages are not given. The primary data provided for one of them strongly suggest that it was infected by a relative at the age of three months.

vaccinated at an early age, but who nevertheless contracted TB. But it does not. Again, if the inoculated subjects are not infected until after the vaccine has taken effect, isolation will make no difference — that is to say, there would be no lowering of the frequency. This is already clear from the fact that, even when the risk of TB is known, isolation is discontinued as soon as the subject is tuberculin positive, i.e., according to the present view when he reacts positively to at least 1 mg Mantoux. The following assumption must therefore be made from the absence of BCG-vaccinated subjects in JORUP's survey and from the decrease in the TB frequency due to isolation and BCG vaccination of children of tubercular mothers in the results of GENTZ and BLUHM — namely, that no children in these groups were inoculated up to and including 1944, which is the last year covered by JORUP's material, and the last before that of GENTZ and BLUHM shows a fall in infant TB. A very strange fluke must be at work here, particularly as there were very few very young infants (thirteen in all) in JORUP's results, collected over a period of five years, for cases of TB contracted during the first three months as a whole; a number which seems even smaller when it is compared with four times as many mothers with active but previously undetected TB who were found in the next five year period, which overlapped the last by one year. At any earlier date, the children of such mothers could not have been isolated, even for only part of the most risky period. Only a small number of the mothers in the above group should therefore be assumed to have infected their consequently non-inoculated children during the first three months of life, particularly as the group must be filled out with children correspondingly threatened by their fathers and other contacts.

Let us now take for a minute the question of the value of general BCG vaccination of the newborn to combat the mortality rate of infant TB, and in particular the rate which JORUP so rightly stresses in the first three months and first half year of life. The most interesting thing to know here is which children fell ill during the second and also the third three months of life,

since these must have been infected before any safeguard in the present accepted sense could have developed.[1]

Neither JORUP (with the above-mentioned exception of three BCG-vaccinated children) nor GENTZ and BLUHM provide primary data of a kind that would enable us to fix the age at which the smitten children were infected. It is therefore impossible to make a further analysis nor, consequently, can the actual infection risks run by uninoculated children during the first three months of life be established. But it must be admitted that, however we look at it, there is a surprising disproportion between the number of TB cases in JORUP's material (which there is every reason to presume fairly complete), the frequency of sources of infection without isolation, the relatively small number of any BCG vaccinations at all among the TB cases, and the chance that all, or nearly all, of those vaccinated at some time during infancy had escaped infection during the incubation period of the vaccine, with the additional chance that all or nearly all of those cases who did not respond actively to 1 mg Mantoux similarly escaped infection. This being so, one ought perhaps to look for a special reason to explain why the BCG-vaccinated are so conspicuous by their absence among the TB cases. The most logical line to take would be to see whether some protection is conceivably developed while the vaccine is still in the incubation stage. This offers a wide perspective in several respects. If this were so, then in the first place a positive reaction to at least 1 mg Mantoux would not necessarily presuppose protection, since the subject would be protected in some way before such a reaction could be demonstrated. It seems, then, to be a question merely of a difference of degree. The protection must be considered to be surer and better if a positive reaction can be established.

This being so, protection could have been accorded to a number of so-called negative subjects also, and conversely, such

[1] In JORUP's later survey, deaths are plainly predominant in the first half year of life. It is, to say the least, doubtful whether the deaths in the first three months have fallen at all since the previous five year period, although the frequency of BCG vaccination of newborns has been doubled many times over.

protection might be prolonged beyond the period when, according to current belief, tuberculin positivity has worn off. This view is not in itself untenable, since according to our present knowledge allergy and immunity to TB do not always coincide. Protection after BCG vaccination would consequently not only set in earlier, but also in far more subjects, and would persist longer than has hitherto been supposed. If this is so, it would obviously be far easier to explain both the very small amount of illness and death from TB in JORUP's BCG-vaccinated material, and the TB statistics as a whole, where numbers are disproportionately low in view of the relatively high percentage of negative reactions and the often comparatively short duration of a positive reaction after BCG vaccination. As can be indirectly deduced, it is otherwise extremely difficult to reconcile the very small number of BCG-vaccinated subjects falling ill as early as the second three months of life with TÖRNELL's results for tuberculin positivity, which results would indicate that about half of all inoculated and subsequently reacting cases may be unsafeguarded from infection right up to the fourth and even fifth months of life. The current view that there is no immunity before the end of the vaccine's incubation period would in such a case have to be revised, and this could hardly fail to have consequences.

It would therefore be interesting to see whether this circumstantial evidence yielded by the human subject is all there is to back up the view both that a certain immunity is possible without demonstrable tuberculin positivity, and that the vaccine provides some protection even during its incubation period. In point of fact it is not all. Further support can be derived from the well-known fact that a previously inoculated spot may show a reaction when the subject is reinoculated because he or she reacted negatively to up to 1 mg Mantoux. This would also tally better with the often surprising frequency of failures in intracutaneous inoculation. When revaccinating four years after the first inoculation of then negative cases, TÖRNELL obtained both local and tuberculin reactions sooner and to a more pronounced degree than on the first occasion. This he takes to indicate a certain degree of (persisting) immunity. The above state of affairs

ties up quite well with experiences from smallpox vaccination. As in the latter case, no so-called negative phase seems to set in with BCG inoculation (WALLGREN 1947 a), and furthermore, so-called immunity reactions to renewed inoculation are, in principle, the rule in certain situations when revaccinating against smallpox (GYLLENSWÄRD 1934 and 1936). Still further support is found in the behaviour of the weight of the above-mentioned BCG-vaccinated children (GYLLENSWÄRD 1949), which seems to show that there is a general reaction in the form of a retarded increase after such inoculation. The importance of a general reaction where immunity is concerned has also been advanced in the studies on smallpox vaccination (GYLLENSWÄRD 1934 and 1936). In the investigation in question, it was particularly in the first three months of life that the children ceased to put on weight after inoculation, and this effect made itself felt no more than a few weeks after inoculation or, in other words, long before the earliest juncture when a positive reaction is wont to appear. The retarding effect also seemed to come out more strongly when the weight was not recorded until four, and still more six weeks after inoculation; that is to say, it increased parallel with the lapse of time during which the inoculation should have been expected to have a successively raised action.

A very important point is that, if protection begins to be formed so early, the result would not only do much to justify WALLGREN'S (WALLGREN 1947 c) recently mooted 'emergency vaccination', i.e. inoculation of tuberculin-negative subjects who have been exposed to infection and cannot be isolated from the source; it would also argue that such vaccination is not only defensible but may even often be expected to achieve some kind of protection, even if the infection has been contracted before the vaccine has had time to set up tuberculin positivity. Vaccination should therefore not be undertaken only in the hope that, by a lucky fluke, infection will not set in until a positive reaction has had time to appear, but in the hope of obtaining some sort of protection even if the infection declares itself in the meantime. This latter hope would be vain if the infection were to come too soon after the inoculation, but gains in strength the longer after

vaccination (in other words, the nearer to the appearance of a positive reaction) the infection waits. In such cases, however, a vaccination of this kind should be the normal procedure. As soon as a TB contact has been ascertained, and a negative reaction established, the suspected subject should be vaccinated with BCG, even if he can be isolated from the known source of infection; nor, as has hitherto been the ruling at least for such cases, should one wait until the incubation period of the possibly virulent TB infection is over. In this case, too, a comparison with smallpox inoculation readily presents itself, even if such comparisons must naturally not be pushed too far. The possible difficulty of determining whether a subsequent positive reaction is due to the vaccine or to a virulent TB infection must be considered only a minor drawback, which in many cases is, anyhow, an inevitable consequence of the wider use of BCG inoculation.

Perhaps it should be stressed that confirmation of the views advanced above would in no way diminish the importance of GENTZ and BLUHM's observations; nor would it lower the need of the most careful TB check on the mothers (and if possible, the entire home surroundings) that these two investigators propose. In any situation, it must take a certain time for the vaccine to produce protection. If, as may be the case in LEVINE and SACKETT's cases, for example, the infection is very early and very severe, no or very inadequate protection will have time to develop. In cases of otherwise early infection, isolation is unavoidable, and must always help until the best possible protection has been obtained. But there is hope for at least some of those where, according to previous conceptions, an infection setting in before tuberculin positivity had been reached would have spelt their doom.[1]

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[1] A striking point in JORUP's last survey is, indeed, that deaths from TB up to and including the first three months of life seem practically without exception to have occurred among those who were not BCG-vaccinated. With all due regard to the probable effect of raised standards of living on resistance to TB, JORUP's results and the catastrophic mortality rate of TB as a whole should show that they do not make any essential difference at these ages.

On the other hand, it is obvious that BCG vaccination can be far more valuable that we have hitherto dared to hope, and the situation is far more promising than GENTZ and BLUHM's Stockholm results would lead us to believe. These results are alarming since, as has already been pointed out, it is hardly possible to predict when it will be practicable to make it a nation-wide concern to keep such checks even on pregnant and recently delivered women — much less, then, on the remaining home milieu of the newborn child. After infancy, the difficulty of avoiding even known sources of infection increases with the age of the child. Whatever practically possible protective measures are taken, it still seems that no small number of those vaccinated at birth or at a later date are liable to infection before a positive reaction is obtained; this is all the more likely if the home surroundings have not been carefully checked. Even when TB is detected, it is often very difficult to say with certainty whether or not a risk of infection can be predicted; this is particularly patent from JORUP's data. It is tragic but true that even an extensive check-up by the clinic may not bring all the TB risks to light, and that even when they are known it is extremely difficult to judge whether or not tubercular persons constitute a danger, and if so, to prevent them from infecting the children. The earlier some protection begins, then, the better, and it is also encouraging to know that such protection often seems possible when, judging by the reaction, the inoculation seems in point of fact to be a complete failure.

In view of the fact that a certain protection exists even before the development of tuberculin positivity it seems reasonable to suppose that protection also remains for some time after the fading of an earlier tuberculin sensitivity, thus increasing the value of BCG vaccination. In this respect also a similarity to smallpox vaccination is striking.

The facts that have been adduced seem, finally, to demand a revision of the value which has hitherto perforce been set on BCG vaccination of the newborn as a weapon in the battle against infant TB, particularly that of the first half year. If a positive reaction to 1 mg Mantoux is not a necessary prerequisite of any kind of protection at all, protection being achieved long before,

and sometimes even without, such a reaction, we gain an inoculative prophylaxis which, in view of the apparently frequent and uncontrollable risks of early infection, is as desirable as it has hitherto been regretfully considered non-existent. Compared with this, the possible retardation of the weight loses importance. Thus, the otherwise inevitable doubt whether the neonatal period is the right time for a first, more general BCG vaccination seems materially swept away, and the choice of this age as the most suitable is given a stronger motivation than has hitherto obtained — over and above the purely practical consideration that it is so easy to get at newborn infants who are born in an institution. It seems, however, that premature and otherwise delicate newborn children should not be inoculated, nor yet older children who are delicate or convalescent, unless there is a special reason (risk of TB); and concurrent inoculation of any other kind should also be avoided.

On the other hand, a check on subsequent tuberculin positivity should not be omitted on that account; on the contrary, it is more necessary than ever, because it is the only practical method we have for proving the inoculation has taken. Similarly, the check-up on TB in the homes of the newborn children should obviously be intensified.

Summary

In spite of the decrease in frequency, TB is still a folk-disease in Sweden. We have no effective means of safeguarding against contracting TB when exposed to infection except preventive BCG vaccination. It has hitherto been supposed that no protective action sets in before a positive reaction to 1 mg Mantoux. According to earlier views, this takes at least six—eight weeks, while half of all those reacting later than this need up to about three—four months. Even where the inoculation takes, then, this period would be unprotected against infection. The possibility of warding off TB by the inoculation of all newborn infants depends to varying degrees on knowing that the risk exists. Such knowledge is essential during the first three months of life, and very important during the

second and possibly even the third three months (= the unprotected period + the incubation period of an infection contracted at the latest possible date during this vulnerable time), the point being that only newborn children known to be threatened by TB are isolated. However, in a recent intensive check-up on expectant and recent mothers in Stockholm, GENTZ and BLUHM found twice as many cases of unmistakably active TB in mothers as were previously known to exist. In a Stockholm material treated by JORUP, children contracting TB during the first half year of life had practically without exception been infected by some member of the family. This state of affairs must be assumed to hold for the whole of Sweden. For this reason, a general BCG vaccination of all newborn children would not be much use without a more intensive check-up on expectant and recent mothers. Such a check-up is particularly necessary when delivery takes place at an institution, in view of the risk of infection to other mothers and children alike. According to GENTZ, nearly half of the young mothers in Stockholm at the beginning of the 1940's were themselves tuberculin negative. To this group of children should probably be added one at least as large, and very likely larger, where the fathers, inmates of the home, and other contacts had active TB eluding the present controls. The entire home surroundings should therefore be more carefully followed up. Facts are given, based on an investigation of the present author (1949) and on data from a work by JORUP (1946), which suggest that the TB of the fathers is less widely known about than that of the mothers. Investigating TB in children under two years, JORUP found the source of infection to be unknown in nearly 30 %, while in more than 30 % it came from older cases under observation, many of which had been diagnosed as not infectious, and in nearly 40 % the tubercle was discovered for the first time. Since, at the present time, isolation is only effected for those BCG-vaccinated newborn children and infants known to be threatened by TB, and since the TB risk is often unsuspected, it means in point of fact that no isolation during the most dangerous period follows vaccination even for perhaps the majority of infants in the most threatened group, i.e. newborn

children of tubercular mothers with definitely active TB. We might therefore expect to find that quite an appreciable number of BCG-vaccinated children were infected before the vaccine took effect, and fell ill and died of TB. This does not seem to be the case, however.

A survey by JORUP of cases of children under two years treated for TB in children's hospitals in Stockholm during the years 1940—44 yielded only three BCG-vaccinated children, and of these possibly only one who had been infected during the incubation period of the vaccine. Nowadays BCG vaccination is very common. In 1947, for example, half of all the children born in Stockholm were vaccinated at birth. In view of the results obtained by JORUP and by GENTZ and BLUHM, it seems hardly likely that almost all non-isolated vaccinees should have escaped infection during these critical months. On the other hand, the total number of children in JORUP's material who contracted TB at an early age is surprisingly small when compared with the number of sources of infection cited by GENTZ and BLUHM. It is therefore conceivable that some protection may start to form quite early in the incubation period of the vaccine, i.e. before the accepted standards of tuberculin positivity have been reached; and, similarly, that some protection still persists for a time after such positivity may have worn off; while, finally, even so-called negative reactions may provide some safeguard. In support of this we advance the known fact that older inoculated areas may show a reaction on reinoculation of the subject dictated by failure to show tuberculin positivity; there is also an investigation by the present author (GYLLENSWÄRD 1949) which seems to demonstrate a reaction in the form of retarded increase in the weight of children vaccinated, as a rule, in the first three months of life. This retarding effect appeared no more than a few weeks after the inoculation — that is to say, long before a positive reaction to even 1 mg Mantoux is customarily demonstrable. Reference is made to the significance of the general reaction when assessing states of immunity after inoculation against smallpox (GYLLENSWÄRD 1934 and 1936). The value of BCG vaccination, then, is greater than has been supposed. If inoculative protection begins

to set in soon after inoculation and can be present even without a positive reaction to 1 mg Mantoux, and if it can be assumed to remain for some time after this reaction is no longer perceptible, this means correspondingly cheerful prospects that extensive BCG vaccination of the newborn will be able to combat TB perhaps as early as the first and second three months of life — which prospects would look very gloomy if assessed on the findings of JORUP, GENTZ and BLUHM, and myself concerning the actual incidence of sources of infection and the chances of tracking them down. And the justifiability of an 'emergency vaccination' (WALLGREN) gains further support. If the vaccine is already taking effect very shortly after administration, the question is raised, at any rate as regards cases where the prognosis is not very encouraging, whether it should not be considered normal, and not merely applicable to cases where satisfactory isolation from the source of infection cannot be arranged, to vaccinate with BCG as soon as possible after infection has been suspected and/or a negative reaction established, without waiting for the end of the virulent infection's incubation period. Furthermore, it gives the neonatal period more to recommend itself as the correct age for a first general BCG inoculation than has hitherto been the case, quite apart from the purely practical consideration that it is so simple to get at newborn children who are born in an institution. As, however, the vaccination seems to some extent to stop the children from putting on weight, premature and otherwise delicate newborn children should not be inoculated unless there is good reason for suspecting danger of TB. The same applies to the inoculation of delicate children and convalescents at later dates, and for the same reason concurrent inoculation of any other kind should be avoided. Furthermore, checking of a positive reaction should also be intensified, even though some inoculative protection is obtained before it sets in. The fact is that, in practice, there is no other method of making sure that some safeguard has been achieved, and the percentage of positive reactions to at least 1 mg Mantoux is cited in the reviewed surveys as varying from 80 % to only 50 % after vaccination of newborns.

Résumé

Jusqu'à présent on croyait que la vaccination ne confère pas d'immunité avant l'apparition d'une intradermoréaction positive pour 1 mg de tuberculine. Si c'était réellement le cas, la vaccination par le BCG des nouveaux nés serait absolument incapable de fournir contre la tuberculose une protection plus grande, durant les trois à neuf premiers mois — étant donné l'apparition lente de la réaction — que celle apportée par l'isolement seul, loin des sources de contagion durant la période sans protection. Seuls les enfants que l'on sait exposés à la tuberculose sont isolés après la vaccination par le BCG. Des recherches indiquant qu'une tuberculose active mais ignorée est fréquente même chez les enfants allaites au sein maternel.

L'auteur montre, cependant, qu'il y a probablement une réaction générale qui suit la vaccination par le BCG des nouveaux nés et apparaît sous forme d'un retard dans l'augmentation du poids. Elle se manifeste déjà quelques semaines après l'inoculation. Référence est donné a des recherches de l'auteur sur la significance d'une réaction générale suivant la vaccination contre la variole. Ainsi, il peut y avoir une immunité augmentant graduellement après la vaccination par le BCG, même avant l'apparition d'une intradermoréaction positive pour 1 mg de tuberculine, et qui persiste quelque temps après que cette réaction positive a disparu. Il peut même y avoir une certaine immunisation lorsque l'intradermoréaction avec 1 mg de tuberculine est restée negative. Cette hypothèse peut s'appuyer sur le fait qu'on trouve rarement des enfants vaccinés par le BCG parmi ceux qui contractèrent la tuberculose et en moururent. L'importance d'un retard pondéral comme contre indication à la vaccination BCG est discutée.

Zusammenfassung

Bisher hat man angenommen, dass die BCG-Impfung keine Immunität gibt, solange die Tuberkulinreaktion für Mantoux (1 mg) nicht positiv ist. Wenn das wirklich der Fall wäre, so ist die BCG-Impfung kaum mehr im Stande, in den ersten drei, — wenn nicht sechs oder sogar neun Monaten, was auf der in

vielen Fällen erst spät auftretenden Tuberkulinreaktion beruht — gegen die Tuberkulose Schutz zu bieten, als es die einfache Isolierung von der Infektionsquelle tut. Isoliert werden nur solche Kinder, bei denen die drohende Ansteckungsgefahr bekannt ist. Man hat jedoch beobachtet und nachgewiesen, dass nicht erkannte aktive Tuberkulose bei den Müttern nicht selten vorkommt. Man sollte deshalb etliche Tuberkulosefälle bei BCG-geimpften Kindern erwarten, die vor dem Tuberkulinumschlag der tuberkulösen Infektion ausgesetzt sind. Dies scheint jedoch nicht zuzutreffen.

Der Verfasser zeigt, dass nach BCG-Impfung im frühesten Säuglingsalter wahrscheinlich eine allgemeine Reaktion auftritt, welche sich in verlangsamter Gewichtszunahme äussert. Diese lässt sich schon einige Wochen nach der Impfung feststellen. Hierbei wird auf die Untersuchungen des Verfassers über die Allgemeinreaktion bei Erzielung der Pockenimmunität nach der Vaccination hingewiesen. Nach der BCG-Impfung folgt also eine allmähliche Steigerung der Immunität, schon bevor die Mantouxreaktion für 1 mg positiv wird, wie auch eine gewisse Zeit nach dem Verschwinden der zuvor positiven Mantouxreaktion noch eine gewisse Immunität bestehen bleibt. Es ist also möglich, dass nach der Impfung eine gewisse Immunität eintritt, auch wenn die gewöhnlich geforderte Tuberkulinempfindlichkeit nicht erreicht wird. Die Seltenheit der Todesfälle bei den BCG-geimpften Kindern stützt die Richtigkeit der obengenannten Auffassung. Die Bedeutung der verlangsamten Gewichtszunahme als Kontraindikation gegen BCG-Impfung wird diskutiert.

Sumario

Hasta ahora se ha creído que la vacunación con BCG no produce inmunidad antes de la aparición de una reacción positiva a 1 mg de tuberculina (Mantoux). Si esto es realmente así, la vacunación con BCG de los recién nacidos es enteramente incapaz de producir mayor protección contra la enfermedad tuberculosa, durante los tres primeros meses de vida — si no es de los seis o nueve primeros meses, debido, en muchos casos, a la reacción tardía

— que la que se puede realizar por el simple aislamiento de las fuentes de infección durante este período sin protección.

Solamente los niños que están amenazados de contraer tuberculosis son aislados después de la vacunación con BCG. Se hace referencia a las investigaciones que han indicado que la tuberculosis activa, pero no reconocida, es frecuente aún en las madres.

El autor muestra, sin embargo, que hay probablemente una reacción general consecutiva a la vacunación que se manifiesta en la forma de un retardado aumento de peso. Esto puede observarse a las pocas semanas de la inoculación. Se hace referencia a las investigaciones del autor sobre la significación de una reacción general después de la vacunación contra la viruela. De este modo puede producirse un aumento gradual de la inmunidad que sigue a la vacunación con BCG y aún antes que 1 mg de tuberculina (Mantoux) produzca una reacción tuberculínica positiva y en este caso se mantiene lo mismo, por algún tiempo, después que la reacción positiva ha desaparecido. Puede haber aún alguna inmunidad que siga a la inoculación en la que la reacción tuberculínica, la naturaleza convencional de la cual está señalada, no ha sido alcanzada. Como soporte de esta suposición existe el hecho poco frecuente de que los niños calmetizados se encuentren entre los que han contraído y muerto por causa de la tuberculosis. Se discute la importancia que puede tener el retardado aumento de peso, como una contraindicación de la vacunación con BCG.

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FROM THE CHILDREN'S DEPARTMENT OF THE STATE HOSPITAL, OSLO.
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Will the Improved Prognosis of Sepsis Neonatorum Be Succeeded by an Increased Number of Cases of Pylephlebostenosis Splenica?

by

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Pylephlebostenosis splenica (p. s.) was previously a rare disease. However, there are circumstances which tend to show that during recent years this disease has appeared with rising frequency.

An examination of the material from the State Hospital, Children's Dep't., seems to confirm this impression. During the period 1925/1945 only three patients were treated for p. s. in this department, while in the three years 1946/1948 nine patients were treated for the same disease.

This increased occurrence provides an opportunity for speculation regarding the cause of the p. s. Many authors state that navel infections and pyogenic infections of the truncus such as furunculosis and osteomyelitical foci are important aetiologic factors in p. s. Thus in his monograph (1927) regarding this disease WALLGREN refers to two cases of his own and four described previously (KLEINSCHMIDT, TÜRK, HART) in which he considers umbilical or neonatal septicopyaemic infection the most obvious aetiological factor.

Consequently we might draw the conclusion that the increased occurrence of pylephlebostenosis is due to the fact that formerly patients seldom managed to recover from such serious pyogenic infections, whereas now, due to modern therapy, they recover to a larger extent. The improved prognosis of sepsis neonatorum may be kept in mind.

Sepsis neonatorum is due largely to pyogenic infections de-

veloped from the navel. Thus in a material from the State Hospital, Children's Dep't., for the years 1946/1948, infected navels were found in twenty out of twenty six cases.

Immediately after birth the umbilical vein, which during the latter part of foetal life ends in the left branch of the portal vein, is obliterated and forms the ligamentum teres hepatis. It is therefore hardly probable that in postnatal infections phlebitic processes in the portal vein area can be thought to have arisen by transmission along the obliterated umbilical vein. It is more probable that the infection has passed through the small parumbilical veins, which also pass through the lig. teres and are connected with the portal vein. The parumbilical veins anastomose on the wall of the abdomen with the vena epigastrica superficialis and profunda and the vena mammaria interna, which empty into the subclavian vein.

Thus pyogenic infections of the navel itself as well as in the wall of the abdomen may easily be thought to give an opportunity for phlebitic processes in the portal vein area.

This also fits in very well with the clinical observation that in serious navel infections one can often palpate a solid infiltrated string from the navel and up towards the epigastrium.

Formerly the prognosis in pyaemic septic infections was very poor. Most patients died so quickly that it was not possible for the characteristic picture of pylephlebostenosis splenica to develop. Modern treatment has altered this circumstance, however, as some figures from the State Hospital, Children's Dep't., will illustrate.

In the period 1925/1945 twenty six patients in all were treated under the diagnosis sepsis neonatorum (septicaemia or septicopyaemia during the first four weeks of life). Twenty of them died shortly afterwards from the infection.

In 1946 we began in this department a systematic penicillin treatment of all cases of sepsis neonatorum. The prognosis for these patients then totally altered, and of the twenty six patients treated during the three years 1946/1948, only six died.

In the course of the first period, 1925/1945, three patients were treated for p. s., while in the course of the second period, 1946/1948, nine patients were treated for the same disease.

If our p. s. material is now perused with special attention to the aetiologic possibility that the increased occurrence of p. s. is due to the improved prognosis of sepsis neonatorum, it appears that of the three patients treated for p. s. in the first period, one, a thirteen month old boy, had an abscess on the left hip when he was four weeks old and in the course of the following two months an abscess on the upper part of the left arm as well as an abscess in the sacral region. The navel was not infected, however. There was no information that the two other patients had had any navel infection or pyaemia (the case reports show that they were examined for this).

In the second period, on the other hand, of nine patients treated for p. s., four had had definite pyogenic sepsis neonatorum which apparently began from the navel.

The case reports of these four patients are in brief as follows.

Case 1. H.H. ♂, b. Dec. 6, 1945. Nothing noteworthy at birth. On the eleventh day there was rubor around the navel, which was infected, fever, and swelling and rubor in the right groin and right heel. In the pus from the navel yellow haemolytic staphylococci were found. The x-ray examination showed osteomyelitis of the pubic bone. The clinical diagnosis was sepsis neonatorum and the patient was given combined sulfa-penicillin treatment.

The temperature fell and the infiltration disappeared. The patient was discharged from the hospital after three weeks. He was then thriving, but it must be noted that the spleen, which during his stay in the hospital had been palpable, was found on discharge to be still the width of one finger below the costal arch.

Apart from the fact that he constantly had slight anaemia, the patient seemed to be in good health and developed normally, until two and one half years later he suddenly began to suffer from melaena and haematemesis. He was admitted to an out-of-town hospital and only a short while afterwards transferred to the Children's Dep't. of the State Hospital. The spleen was then palpable the width of five fingers below the costal arch. There was ascites. Hgb. 55 %; RBC 3.32 mill.; WBC 4 900; thrombocytes 153 000. Normal prothrombin time, bleeding time, and coagulation time. X-ray of oesophagus: varices in the lower part.

The patient was transferred to our Surgical Dep't. under the diagnosis p. s. Splenectomia + splenorenal anastomosis were performed and the patient was discharged in good health.

(The pat.-anat. examination of the spleen showed an enlarged spleen with fibrosis, perisplenitis, reactive changes, and congestion.)

Case 2. O.H. ♂, b. May 12, 1947. The child's birth was normal and uncomplicated. On the eighth day of life the navel was red and showed pus. At the same time swelling and rubor on both big toes were observable. The abdomen was meteoristically distended and the child's bowel movements were green and frequent. The patient did not thrive and was consequently admitted to this department on the seventeenth day of life. The navel then had a coating of pus with a central necrosis. Over the ground-phalanges of both big toes abscesses were found. These were incised. Cultivation of the pus revealed haemolytic streptococci. The spleen and the liver were palpable the width of two—three fingers below the costal arch.

The clinical diagnosis was sepsis neonatorum and the patient was given combined sulfa-penicillin treatment, but in spite of this in the beginning his general condition was poor. A phlegmon of the wall of the abdomen developed and there were also symptoms of meningitis with increased cell numbers in the spinal fluid (128/3 cells per mm^3). The penicillin doses were increased and gradually his general condition improved. The infiltrations and the meningitic symptoms disappeared and the patient was discharged after twenty three days. He was then thriving and clinically free of symptoms. Eleven months later he was again admitted to this department for observation due to the fact that his mental and physical development was poor. Encephalography indicated that brain atrophy with hydrocephalus e vacuo was present. It was also found that the patient had ascites. The spleen was palpable the width of four—five fingers below the costal arch and the liver the width of two fingers below the costal arch. Hgb. 85 %; RBC 5.02 mill.; WBC 6 200; thrombocytes 231 000. Prothrombin time, serum colour, serum proteins normal. Takata's reaction negative. Bz. in faeces negative.

X-ray examination of the oesophagus showed varices in the lower part.

The condition was perceived to be p. s., but on account of the patient's oligophrenia it was decided that no operation was indicated.

Case 3. T.R. ♂, b. April 13, 1946. The child's birth was normal and uncomplicated. On the fourth day the navel came off. From the eighth day there was navel pus. In the course of the following eight days the navel became clean and dry, however. A week later the patient appeared weak and was unwilling to suck. In the course of the following days an abscess developed on the right side of the thorax and some days later a pyartrosis of the left knee joint. The abdomen was much distended. The liver was palpable the width of two fingers below the costal arch. The spleen was hard and palpable the width of two fingers below the costal arch. In blood culture as well as in the pus from the abscesses haemolytic streptococci were found. Diagnosis: sepsis neonatorum.

The abscess was incised, the knee joint punctured, and the patient given sulfa-penicillin treatment.

The patient was discharged after twenty one days and was then clinically free of symptoms, apart from the fact that the spleen was palpable the width of two fingers below the costal arch.

The patient has subsequently been under control as an outpatient. He has thrived the whole time, although the spleen has remained enlarged.

The blood status has been as follows:

	Hgb. %	RBC per mm^3	WBC per mm^3	Thrombocytes per mm^3	SR
On Discharge 20.6. 46	100	4.20 mill.	12 700		22 mm/hr.
Control 9.12. 46	85	4.12 »	7 200	150 000	22 »
» 13.5. 46	80	3.80 »	5 000	83 000	8 »
» 28.8. 46	76	4.02 »	5 600	257 000	16 »
» 3.12. 46	70	4.20 »	9 200	126 000	25 »
» 26.4. 47	71	4.84 »	4 500		
» 30.11. 47	80	5.12 »	5 800	543 000	14 »

On Nov. 30, 1948, the findings were as follows: prothrombin time 24 sec. (contr. 18 sec.), coagulation time 1 ½ min., bleeding time 2 min., serum colour 2, Takata's reaction pos. (precipitation in four glasses), thymol reaction 0.18.

The suspicion that the patient had p. s. was confirmed by x-ray examination, which showed an enlarged spleen with quite a considerable development of varices in the oesophagus.

The patient will be transferred for surgical treatment.

Case 4. Br.B. ♀, b. May 6, 1946. Normal uncomplicated birth. On the twelfth day the navel was purulent and rubor and swelling of the right hand joint developed with an abscess. The latter was incised. The patient was treated with penicillin in an out-of-town hospital. She was discharged after one month, allegedly well. She was well for about one and a half years, when suddenly one evening she had melaena and discharged about one cupful of tar-like faeces. In the next three days this was repeated three times and the patient was admitted to an out-of-town hospital. She was exhausted, with a Hgb.% of 25 on admittance. She was treated with four blood transfusions in all and discharged after one month. Six months later the same thing happened. This time an explorative laparatomy was performed, as a bleeding ulcer in Meckel's diverticulum was suspected. No cause of the haemorrhage was found, however. The patient was treated with Fe, but no blood transfusions were given. During her stay in the hospital, where she remained for two

and one half months, it was not possible to bring her Hgb.% above 60 in spite of the fact that she had no new haemorrhages.

Shortly after her return home she again had haemorrhages per rectum and was admitted to the State Hospital, Children's Dep't., on Oct. 8, 1948. The spleen was then palpable the width of two fingers below the costal arch. The liver was not palpable.

On admission test results were as follows: Hgb. 77 %; RBC 4.98 mill.; WBC 13 300; thrombocytes 175 000. Prothrombin time 18 sec. (control 16 sec.); serum colour 2, Takata's reaction neg. (precipitation in two glasses); thymol 0.20. Meinicke's reaction neg. X-ray examination showed large varices in the lower part of the oesophagus.

The patient was transferred to the surgical department for surgical treatment under the diagnosis p. s. Just before the operation she again had severe melaena and haematemesis. This was repeated several times and her Hgb.% was reduced to 22 %. At the same time her spleen decreased in size. Owing to her poor general condition surgical treatment was postponed. Repeated small blood transfusions of 50 ml were given as well as Fe per os. The Hgb.% increased slowly and her general condition improved. During this period of time the patient probably was exposed to a pertussis infection. As soon as she has recovered from this infection she will be surgically treated.

These four cases have in common the fact that all went through a serious septic infection which probably started from the navel. Before the days of sulfa treatment and penicillin probably none of these infants would have survived their serious infections. In all four cases a typical p. s. picture developed in the course of a couple of years.

Case 3 is characteristic. This patient thrived after being »cured» of his sepsis neonatorum, but on account of his previous disease and the fact that on discharge from this department his spleen remained enlarged, he was kept under careful observation. His constantly enlarged spleen, slight anaemia and leukopenia, and to some extent his thrombocytopenia maintained the suspicion that he suffered from p. s. This diagnosis was confirmed by x-ray examination, which showed varices in the oesophagus. Up till now these varices have not given any symptoms in the form of haemorrhages.

Experience has shown that the results of surgical treatment are best if an operation can be performed at an early stage, i.e.

before the liver has been damaged and before the congestion in the veins has caused injury to the vessel wall.

The prognosis in this case will probably be relatively good, as even now the boy may have a splenectomy performed, possibly in connection with a splenorenal anastomosis.

Conclusion

Septic infections, especially serious navel infections, probably play an important aetiological part in the development of p. s.

During the last three years a strikingly large number of patients suffering from this disease has been treated at the State Hospital, Children's Department.

This is assumed to be due to the fact that while formerly most of the serious cases of sepsis neonatorum died in a short period of time, it is now possible by the use of modern treatments to discharge most of these patients apparently cured.

Our cases have shown that in any sepsis starting at the navel the possibility of subsequent p. s. should not be overlooked. Therefore in the following years the patients should be controlled specially regarding this.

Summary

The patients »cured» of sepsis neonatorum should in the following years be examined with special regard to pylephlebostenosis splenica, so that if necessary they can be treated surgically before the liver is damaged and before congestion of the veins has caused irreparable injuries endangering life through haemorrhages.

Résumé

Les malades »guéris» d'une septicémie du nouveau-né doivent être contrôlés dans les années qui suivent avec une attention spéciale pour le risque d'une pylephlébostenose splénique, afin qu'en une telle éventualité, le traitement chirurgical puisse être entrepris avant que le foie ne soit lésé et que la congestion des veines n'ait causé d'irréparables dommages faisant courir durant toute la vie des risques d'hémorragie.

Zusammenfassung

Diejenigen Patienten, die von einer Sepsis neonatorum »geheilt» wurden, sollten in den folgenden Jahren kontrolliert werden mit besonderer Rücksicht auf eine Pylephlebostenosis splenica, damit sie gegebenenfalls chirurgisch behandelt werden können, bevor die Leber geschädigt ist, und bevor die Überfüllung der Venen irreparable Schäden angerichtet hat, die das Leben durch Hämorrhagien bedrohen.

Sumario

Los pacientes que se han restablecido de una sepsis neonatorum, deben en los años subsiguientes controlarse, pensando en una posible pilo-flebo-estenosis espelenica, de manera que puedan ser tratados quirurgicamente antes de que el higado se lesione, y antes de que la congestión venosa produzca lesiones irreparables, que de origen a hemorragias que pongan en peligro la vida del enfermo.

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FROM THE CHILDREN'S CLINIC, UNIVERSITY OF HELSINKI.
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On Intrathecal Irritation Produced by Penicillin and Physiologic Sodium Chloride Solution

by

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In recent literature there are numerous reports pertaining to the irritant effect of penicillin (P.) in intrathecal administration. The general way of using P. is to dissolve it in physiologic sodium chloride solution (0.85—0.9 %), which is then injected intraspinally or intracisternally in amounts of 5 to 40 ccm. The Germans MADER and SAENGER observed, however, that mere physiologic salt solution sometimes produced strong symptoms of irritation, several of which were unmistakably similar to those described as due to P. With the aim of throwing light upon this question we have undertaken some experiments on six mentally defective infants.

To avoid injuries, intraspinal technique was used throughout in the experiments. The syringes were of common metal and glass sterilized by boiling in water from the main. P. was crystalline G-penicillin. When using small volumes, a strong P. solution was diluted in the syringe with 5 ccm spinal fluid; this was then reinjected into the lumbar canal. Attempts were generally made to inject as much fluid as had been removed. In order to avoid irritation punctures were not made at shorter intervals than twenty four hours.

Case Reports

1. Rec. No. 2611/48. A.F., aged eleven months. Weight 6 kg. Idiotia mongoloidea.

On Aug. 5, 1948, 5 ccm spinal fluid was replaced with 0.9 % salt solution. After fifteen hours the temperature was 38.2° C. The infant was contented and ate very well. The spinal pressure was approximately

normal, the fluid purulent, cell count 8 700/ccm. Bacteria culture: 0. For other changes see Table 1.

On Aug. 17 5 ccm spinal fluid was compensated with sodium chloride to which had been added 10 000 units of P. After eight hours the temperature was 38.5 C. The patient was sleepy and there was some slight rigidity of the neck. Aug. 18: afebrile, reacting in the usual way. The spinal fluid was purulent, the cell count 1 654. Bacteria culture: 0. On Aug. 24 an intrathecal injection of 10 000 units of P. was administered in 0.2 ccm saline solution. After eight hours the temperature was 38.5 but otherwise there was nothing noteworthy. The patient was afebrile after twenty four hours. Cell count 80. Patient looked quite well. On Aug. 31 10 000 units of streptomycin was injected in 0.2 ccm saline solution. The cell count, at the moment of injection 53.3 per cmm, was only 18 on the following day. Bacteria culture: 0. The patient looked well the whole time.

Table 1

A. F., aged 11 months. Rec. No. 2611/48.

Date	Leukocytes/ cmm	Erythrocytes/ cmm	Nonne	Pandy	Cl mg% (NaCl)	Sugar mg%	Treatment
5.8	0.6	0	—	—			5 ccm phys. saline solution
6.8	8 700	0	+	+			
7.8	2 032	335	+	+			
9.8	31.3	0					
10.8	10	137					
12.8	18	356	—	+			
17.8	4.3	0	—	—	743	46	10 000 penicillin units in 5 ccm saline solution
18.8	1 654	203	+	+	755	51	
19.8	613	64			754	55	
20.8	28.3	7.3			760	51	
21.8	16	6			755		
24.8	4	0	—	—	766	47	10 000 penicillin units in 0.2 ccm saline solution
25.8	80	9			760	43	
26.8	34.6	1.3			760	36	
27.8	168	5			760	65	
28.8	13.3	9.3			755	42	
31.8	53.3	5.3			731	63	10 000 streptom. units in 0.2 ccm saline solution
1.9	18	5			731	42	

2. Rec. No. 2671/48. S.-E.S., aged three years two months. Weight 12 kg. Idiotia mongoloidea.

On Aug. 11, 1948, 10 000 units of P. were administered intrathecally in 0.2 ccm saline solution. The subsequent condition was good, with no rise in temperature. On the following day the cell count in the spinal fluid was 17.

On Aug. 20 the same amount of P. was administered, dissolved in 5 ccm saline solution. After eight hours the temperature was 38.5, neck rigidity was fairly pronounced, and there was increased sensitiveness in the whole body. The symptoms receded after twenty four hours. There were 170 leukocytes per cmm of spinal fluid. Bacteria culture: 0.

On Aug. 28 5 ccm saline solution was administered. After six hours the temperature was 40.2. Strong rigidity of the neck and tenderness. The patient was apathetic and looked ill. In twenty four hours the temperature was still 39.1. The other symptoms receded. Twenty four hours after the injection the spinal fluid was purulent, the cell count 2 848. Bacteria culture: 0.

Table 2

S.-E. S., aged 3 years 2 months. Rec. No. 2671/48.

Date	Leukocytes/ cmm	Erythrocytes/ cmm	Nonne	Pandy	Cl mg% (NaCl)	Sugar mg%	Treatment
11.8	4.6	150	—	—	760	150	10 000 penicillin units in 5 ccm saline solution
12.8	17	474	—	+	743	96	
14.8	8.6	7 510				81	
16.8	9.6	429				88	
17.8	17.6	7 700					
20.8	11.6	548			731	110	10 000 penicillin units in 5 ccm saline solution
21.8	170	2 357			672	89	
22.8	64.7	6			592	69	
24.8	2.0	666			684	63	
26.8	64	4 245			696	81	
28.8	42.6	2 506	+	+	714	45	5 ccm phys. saline solution
29.8	2 848	1 194				110	
30.8	376	1 616			702	70	

3. Rec. No. 2696/48. H.P., aged two years and six months. Weight 14 kg. Debilitas mentis.

On Aug. 18 10 000 units of P. was administered intrathecally in

0.2 ccm saline solution. The condition did not change at all. No febrile reaction. After twenty five hours there were 32 and after forty eight hours 69 cells in the spinal fluid, but erythrocytes were found every time, also when injecting P. Bacteria culture: 0.

Table 3

H. P., aged 2 years 6 months. Rec. No. 2696/48.

Date	Leukocytes/ cmm	Erythrocytes/ cmm	Nonne	Pandy	Cl mg% (NaCl)	Sugar mg%	Treatment
16.8	0.3	4 700			725	64	10 000 penicillin units in 0.2 ccm phys. saline solution
17.8	32	3 700			760		
18.8	69	1 100			760	67	
19.8	2.0	3 114			749	81	
20.8	0.6	23			748	60	

4. Rec. No. 2889/48. M.-L.V., aged one year six months. Weight 8 kg. Idiotia.

On Sept. 22, 1948, 5 ccm spinal fluid was replaced with 9 % salt solution. In six hours the temperature was 39.0 and in twenty four hours still 37.5. For a period of about twenty four hours there was slight rigidity of the neck, but the general condition was good. After twenty four hours the leukocyte count in the spinal fluid was 9 200 and the fluid was purulent but there was no increased pressure. Bacteria culture: 0.

Table 4

M.-L. V., aged 1 year 6 months. Rec. No. 2889/48.

Date	Leukocytes/ cmm	Erythrocytes/ cmm	Nonne	Pandy	Cl mg% (NaCl)	Sugar mg%	Treatment
22.9	0		—	—	737		5 ccm phys. saline solution
23.9	9 200			+	766		
25.9	114	186	—	+	761		
27.9	21		—	+			20 000 penicillin units in 0.2 ccm dist. water
28.9	24.2	26.6	—	—	749		
30.9	20		—	—	766		
2.10	0		—	—	766		
6.10	2.3				873		

On Sept. 27 20 000 units of P. was administered in 0.2 ccm dist. water. There was no febrile reaction. The condition was very good again. The number of cells in the spinal fluid increased within twenty four hours from 21 to 24.3. Bacteria culture: 0.

5. Rec. No. 3263/48. H.P., aged three years. Weight 13 kg. Idiotia.

On Oct. 6, 1948, intrathecal administration of 5 ccm modified Ringer's solution (see below (pH 7.4)). There was no subsequent change in the general condition. In six hours the temperature was 38.0. In twenty four hours the spinal fluid pressure was normal, cell count 60. Bacteria culture: 0.

On Oct. 11 an application of 5 ccm saline solution. Again no change in the condition. After six hours temperature 37.8. After twenty four hours cell count 106, pressure normal. Bacteria culture: 0.

On Oct. 14 a repeated administration of the same quantity of saline solution as above. Condition still remained unchanged. Cell count on the following day 76, normal pressure. Bacteria culture: 0.

On Oct. 19 20 000 units of P. administered in 0.5 ccm saline solution. Condition good, no febrile reaction. In twenty four hours the cell count in the spinal fluid was 2.3.

Table 5

H. P., aged 2 years 11 months. Rec. No. 3263/48.

Date	Leukocytes/cmm	Erythrocytes/cmm	Nonne	Pandy	Cl mg% (NaCl)	Sugar mg%	Treatment
6.10	0.6		−	−	731		5 ccm modified Ringer's solution
7.10	69	12.6	−	(+)	720	76	
9.10	53	10.3	(+)	+			
11.10	27	5.6	−	+	696	87	5 ccm phys. saline solution
12.10	106		−	+	743	45	
13.10	17.3	2.6	−	−	684	59	
14.10	20	11 200	+	+	725	58	5 ccm phys. saline solution
15.10	76.6	2 200	−	+	737		
19.10	1.3	4.0	−	−	737	58	20 000 penicillin units in 0.5 ccm phys. saline solution
20.10	2.3	1	−	(+)	714	59	

6. Rec. No. 3184/48. A.P., aged two years and four months. Weight 10 kg. Idiotia.

On Oct. 4, 1948, 5 ccm spinal fluid was compensated by »modified

Ringer's solution». There was no reaction. On the following day the pressure of the spinal fluid was unchanged, cell count 112.

On Oct. 8 the procedure were repeated with physiologic salt solution, some of which trickled out as the syringe was removed prior to withdrawing the needle. After twelve hours the temperature was 37.5; the patient was otherwise asymptomatic. Cell count on the following day 116. Bacteria culture: 0.

On Oct. 11 the proceedings were repeated. Again there were no symptoms, aside from a temperature of 38.8 after six hours. The cell count on the following day was 1 420, the fluid turbid, the pressure unchanged.

On Oct. 18 10 000 units of streptomycin was administered into the spinal fluid in 0.5 ccm saline solution. No symptoms. Cell count increased within twenty four hours from 6.6 to 9.6.

On Oct. 20 20 000 units of P. in the same amount of saline solution as above. No symptoms. Cell count on the following day 11.7.

On Oct. 26 50 000 units of P. in 0.5 ccm saline solution. The drug was applied at 9 a.m. Immediately afterwards the patient turned pale and began to vomit. At 11 a.m. the child was unconscious and cyanotic and respiration was spaced and ratling. The left pupil was sometimes unmistakably larger than the right, with nystagmus to the right. Reflexes vivid. Evident hyperaesthesia. No rigidity of the neck. Pulse rate slow, but became rapid on stimulation with coffein. In the spinal puncture a few drops of fluids were withdrawn which were blood-tinged at first but clear afterwards, with a leukocyte count of 44.3. Bacteria culture: 0. At 11.30 spasmodic contractions of the right eye iris. Twitching in corners of the mouth, hiccough. Temperature 37.1. 12.00 noon colour again became faintly cyanotic. Twitchings, especially in upper right limb, chin, and eyebrows. Then for a period of about ten minutes violent twitching spasms of the whole body. Received two suppositories containing sodium diaethylbarbiturate and heroin. Mucous foam from the nose. Administration of oxygen, stimulants, and magnesium sulfate. At 12.55 temperature 39.7. At 2 p.m. still pale, with a rapid pulse rate. Temperature 40.4. Respiration very slow. Administration of tepid bath. After this the child gradually began to pick up. The left pupil remained small the whole evening, while the right was maximally distended. They did not react. At 3 p.m. the nystagmus had disappeared. The limbs were soft. Reflexes continually rapid. Breathing was somewhat quickened, the pulse rate slower. At 9 p.m. the temperature was 37.1.

On Oct. 27 at 9 the general condition was normal, aside from the patient's being more sleepy than usual, perhaps partly in consequence of the hypnotics administered the day before. The tendon reflexes were still rapid; there was a slight clonus achilli. Both pupils were of the

same size, fairly small, reacting in the usual way. The cell count in the spinal fluid was 20. The patient continued tired and apathetic for about a week, but otherwise did not exhibit any symptoms.

Table 6

A. P., aged 2 years 4 months. Rec. No. 3184/48.

Date	Leukocytes/cmm	Erythrocytes/cmm	Nonne	Pandy	Cl mg% (NaCl)	Sugar mg%	Treatment
28.9	1		—	—	749	45	
4.10	10.3	41			766	58	5 ccm modified Ringer's solution
5.10	112	2 938	+	+			
7.10	10	27.6	—	—	725	62	
8.10	76	870	+	+			5 ccm phys. saline solution — part trickled out again
9.10	116	2.3			749	75	
11.10	48	60	—	+	708	63	5 ccm phys. saline solution
12.10	1 420		+	+	743	43	
13.10	137.3	13 000	+	+	702	55	
15.10	56.6	378	—	+	725		
18.10	6.6	7	—	—		57	10 000 streptom. units in 0.2 ccm phys. saline solution
19.10	9.6		—	—	766		
20.10	1.6	2.3	—	—	708	55	20 000 penicillin units in 0.5 ccm phys. saline solution
21.10	11.7	109	—	—	720	52	
26.10 at 9.00 a.m.	2	1 004	—	+	761	52	50 000 penicillin units in 0.5 ccm phys. saline solution
at 11.45 a.m.	44.3	2 840					
27.10	20	1 760			804		
28.10	28.3	1 028		—	825	56	

Discussion

If we begin by studying the effect of the physiologic saline solution, we note that when it was administered intrathecally it regularly produced an increase of cells in the spinal fluid of up to 9 200 after twenty four hours. The reaction was not equally

violent in every case, the lowest cell count being 106. Simultaneously with the increased cell count the temperature rose to as much as 40.2 C., although not regularly. In addition three cases out of seven had rigidity of the neck and one had increased sensitiveness in the whole body. The »modified Ringer's solution» (a solution prepared by the hospital laboratories to imitate the composition of spinal fluid — this subject will be dealt with in another paper) also produced an increase in the cell count, although not equally pronounced, in the two cases where it was used. Owing to the slightness of the material, it is best at present not to draw any conclusions on the basis of it. The results are consistent with those previously obtained by MADER as well as MADER and SAENGER. As found by these authors also, the symptoms were very transient and did not cause any particular distress. It is evident that the intrathecal area is, in some cases at least, rather sensitive to the introduction of foreign solutions.

In the two cases where P. was dissolved in 5 ccm saline solution, i.e. the same quantity as was used in the preceding tests, there was a corresponding irritation, although the increase in the number of cells was less than when mere saline solution was administered. P. alone dissolved in 0.2—0.5 ccm saline solution or distilled water did not, on the other hand, produce any noteworthy effects. In two of our cases (4, 5) it is not appropriate to speak of any increase in the cell count and in the others the reaction was also unmistakably weaker than when sodium chloride was used. The highest cell count in twenty four hours was 80/cmm. The febrile reaction confined itself to the case just mentioned, 38.5 C. (rectal). All this in spite of the circumstance that when P. was mixed in the syringe with spinal fluid it reached the canal in concentrations of 2 000—4 000 units per ccm. According to several workers the use of stronger concentrations than 1 000 units per ccm should be avoided (ERICKSON AND ASSOCIATES, GASSER AND ASSOCIATES, SIEGAL). In one case only (6), in which a P. dose of 50 000 units in all was administered to an infant weighing 10 kg, did unconsciousness and violent convulsions ensue, but it is noteworthy that even in this case the cell count in the spinal fluid had a fully insignificant increase.

When considering the work of earlier authors[1] we must distinguish between research carried out with healthy individuals, i.e. not suffering from meningitis, and the experiences obtained with those affected with the disease. RAMMELKAMPF and KEEFER administered 10 000 units of P. in 10 ccm 0.85 % sodium chloride solution to an epileptic. The cells in the spinal fluid increased up to 4 170 and for a period of twenty four hours the patient had headache and vomiting, but no temperature nor rigidity of the neck. Another patient, suffering from rheumatic arthritis, was given 5 000 units dissolved in 5 ccm of the said solution. The consequence was a slight headache and an increase in cells to 740. In both cases the symptoms may have been due solely to sodium chloride. We could not ascertain any headache in our cases, but all our subjects were unable to speak. On the other hand it is known that a simple normal spinal puncture can produce even fairly intense headache for a number of days. PILCHER and MEACHAM injected penicillin into healthy dogs by nuchal puncture and pleocytosis ensued in every instance. It is interesting to note that in a dog who was administered 500 units in 1 ccm saline solution, the cell count rose to 3 000, whereas two dogs who received the same P. dose in 2 ccm saline solution had corresponding counts of 16 000 and 19 500. This also suggests that saline solution has an irritant effect, although the workers paid no attention to it. Using intracisternal puncture ZELLWEGER injected three idiot children with 10 000 units each of P. in 10 ccm saline solution. Here also we might consider the symptoms as due, at least in two instances (Cases 2 and 3), to the sodium chloride solution. Collapse manifested in the third case in addition to an increased cell count might have been induced by the puncture as such. It is difficult to assess the P. effect.

BRÆSTRUP has published four cases, none of which apparently had meningitis. The symptoms manifested in them in association with intrathecal therapy were fully consistent with those produced by us in our administrations of mere saline solution.

JEPSON and WHITTY performed tests on adults who had been

[1] For general surveys of the use of penicillin in meningitis or otherwise for intrathecal administration see SCHMIDT (1947) and WYKE (1947).

given 10 ccm P. solution intraspinally. While the solution was fresh the reaction of the spinal fluid was strikingly weak, irrespective of whether distilled water or saline solution was used as dissolvent. In addition, their tables appear to indicate that the use of a metal and glass syringe is in itself productive of irritation as compared with a glass syringe, a circumstance which has been overlooked by other workers.

Still, it may be regarded as certain that a sufficiently massive amount of P. tends to produce irritation of the cerebral cortex. This is indicated by our Case 6, where a child aged two years and four months and weighing 10 kg lost consciousness two hours after the injection, had violent convulsions, etc., although the cell count in the spinal fluid was not significantly increased. This is a circumstance particularly noteworthy because of the absence of meningeal irritation. The danger is, of course, much greater if we use intracisternal administration, in which distribution of the concentration in the whole spinal fluid and especially in the brain area is much stronger and more even. Among earlier investigators, WALKER, JOHNSON, and KOLLROS and WALKER found that P. injected into the cortical layer of the monkey through a trepanation opening produced myoclonic spasms and convulsions. The threshold of irritation for impure and on the other hand crystalline P. is the same and proportional to the antibiotic power, disappearing with it, e.g. when the solution is boiled or sterilized by the autoclave. Similar results were obtained by BORKOWSKY and FORSTER in their experiments with cats. According to NEYMANN 20 000 P. units in the adult occipital cortex produce changes on the electroencephalogram, and 10 000 units in the vicinity of the infant motor area — in addition to twitchings of face and hands of three hours' duration. NEYMANN, HEILBRUNN, and YOUMANS, who injected P. intracisternally into dementia paralytica patients, also observed muscular twitching and spasms subsequent to repeated daily injections over a period of up to two weeks. A patient who was given 100 000 units reacted after only three hours.

It is evident that sensitivity varies greatly in different individuals. An example is provided by ABBOT's experiences with

wartime brain injuries, in which he injected into the brain wound itself 50 000 units of P. in 1 ccm sodium chloride. Several patients received in addition 25 000—50 000 units by intracisternal application; one case received 100 000 units altogether; and only this last-named case exhibited slight and transient symptoms of irritation. WEICHARDT gave a patient with paralysis generalis an intrathecal injection for ten days, gradually increasing the dose from 12 500 to 100 000 units without eliciting any noteworthy symptoms. — An important factor in every instance is of course the purity of the P. preparation. At present, however, the crystalline substance is obtainable everywhere. Some symptoms observed by earlier workers, e.g. ROSENBERG and ARLING, may have been due to impurities.

As we have already mentioned, the question of meningitis is a different matter. There are authors, such as HOYNE and PRICE and HODGES, who consider intraspinal therapy generally unnecessary. Although P. administered intramuscularly or subcutaneously does not, in a normal individual, reach the spinal fluid, this is still the case to some extent in meningitis (COOKE and GOLDRING; ROSENBERG and SYLVESTER; WALKER and JOHNSON; cit. by WYKE). Secondly, they consider it sufficient that the P. level rise in the vascular system of the meninges themselves, these being primarily inflamed. The majority, however, seem to be of the opinion that in severe pneumo-, staphylo-, and streptococcal infections it is advisable to adopt intrathecal therapy parallel with other modes of administration. In any case, abundant bacteria and endotoxin amounts are found in the spinal fluid as well.

Several workers mention irritation associated with intrathecal therapy (ERICKSON AND ASSOCIATES, GASSER AND ASSOCIATES, JOHNSON and WALKER, KLESSENS, MORGINSON, SCHMIDT, SMITH AND ASSOCIATES, SWEET AND ASSOCIATES, etc.). Many of the symptoms described by them may be due to meningitis as such or may be produced by the sudden liberating of abundant endotoxin amounts after initiation of the P. treatment. Although it is evident on the basis of WALKER's (1947) monkey experiments that P. can cause radiculitis, myelitis, and thickning of the lepto-

meninges, it appears as if the large scar formations in the leptomeninges described by e. g. BAILEY were due to the thick purulent exudate already present at the moment of beginning treatment and subsequently organized. SIEGAL has described transversal myelitis developed during interspinal P. therapy and pneumococcal meningitis which does not belong to the clinical picture of acute purulent meningitis. He compares it to paraplegia observed before at the time of serum therapy, but also remarks, believing it to be due perhaps to therapy, that previously cases of pneumococcal meningitis frequently died even before that stage and therefore it is not possible to make comparisons.

When considering the treatment of meningitis, we do not feel it has been evidenced that intraspinal administrations of P. in moderate doses have a noxious effect. To our knowledge, there are no investigations which make it clear how massive the doses must be in order to raise the antibiotic effect to a sufficiently high level. In all probability our applications of 10 000—20 000 units are sufficient for children, if we take into consideration that the amount of spinal fluid in the adult is about 110 ccm (GASSER). According to our experiments these doses do not involve the least danger. In addition, the inflammation of the brain membranes in meningitis prevents P. from being dialyzed through them into the cerebral cortex, and therefore more massive doses are needed to produce symptoms of irritation than if the meninges are sound (WALKER AND ASSOCIATES). This is also supported by wide clinical experience. There are numerous descriptions in the literature of intrathecal administration of 40 000—50 000 units to adults and even children in the management of meningitis (GOTTLIEB and FORSYTH, GERRAD, WYKE, etc.). As an extreme case mention may be made of an adult patient of REULING's and CRAEMER's, who in consequence of an error was subjected to 500 000 units. i.e. ten times the dose intended. In spite of the twitchings and spasms she suffered from for the next eight hours, she later made a complete recovery.

It is difficult to assess the effect of sodium chloride in meningitis. The circumstances are different for the same reasons as where P. is involved. It can evidently be used with much less

circumspection than if the meninges are sound. NISSIM's experiments with washing out the spinal canal with Hartmann's solution point in this direction. Yet there is no doubt that it is always safer to use a solution which is more physiologic to the subarachnoidal space than mere »physiologic salt solution». We shall continue our research along these lines.

Brief mention may be made, without any reference to earlier literature, to the fact that streptomycin dissolved in 0.2 ccm saline solution and administered by our method did not produce any symptoms or irritation whatever.

Summary

The effects on six subjects of intraspinally-injected penicillin and physiological saline solution have been investigated. 10 000 to 20 000 units of penicillin in 0.2—0.5 ccm saline or distilled water did not cause notable irritation. 50 000 units of penicillin in 0.5 ccm of saline produced symptoms of strong cerebral irritation but no increase in the cells of the spinal fluid. 5 ccm of physiological saline solution alone produced in all cases an increase in the cells of the spinal fluid and a rise in temperature. Earlier reports of irritation symptoms claimed to be produced by intrathecally injected penicillin are discussed and it is concluded that some of these symptoms were probably caused by use of the saline solution as a solvent.

Résumé

Sur l'irritation intrathécale produite par la pénicilline et par une solution physiologique de chlorure de sodium

On a fait des recherches sur les effets de la pénicilline et d'une solution saline physiologique par injection intrathécale sur 6 enfants.

10 000 à 20 000 unités de pénicilline dissoutes dans 0.2 à 0.5 cm^3 de solution physiologique saline ou d'eau distillée ne produirent aucun symptôme clinique d'irritation. Un seul cas présenta une température rectale de 38.5°, 6 heures après l'injection. Dans deux cas sur 6, on ne décela pas d'accroissement du nombre des cellules du liquide céphalo-rachidien. Les autres

eurent des nombres de cellules insignifiants. Le plus haut dénombrement de cellules fut de 80 par cm³.

Du chlorure de sodium (5 cm³) produisit régulièrement un accroissement des cellules, le plus haut compte de cellules devenant 9 200 par cm³ en 24 heures. Il y eut une élévation de température dans chaque cas, la plus haute étant de 40.2° (rectale). Trois cas montrèrent de plus une rigidité passagère de la nuque et l'un d'entre eux eut une hyperesthésie généralisée.

De la pénicilline dissoute dans 5 cm³ de chlorure de sodium causa les mêmes réactions que le seul chlorure de sodium.

50 000 unités de pénicilline dans 0.5 cm³ de solution saline produisirent une perte de conscience durant les deux heures qui suivirent l'injection, ainsi que de violentes convulsions et des spasmes dans tout le corps. La température s'éleva à 40.0°. Les symptômes durèrent 24 heures.

10 000 unités de streptomycine dans 0.2 cm³ de chlorure de sodium ne donnèrent lieu à aucune réaction.

Les réactions d'irritation décrites par les auteurs précédents comme dues à la pénicilline sont discutées, et l'on émet la théorie que la majorité d'entre elles sont probablement dues au chlorure de sodium employé comme dissolvant. Les auteurs ont l'impression que la pénicilline, quand elle est correctement administrée et dosée, n'est pas un agent dangereux dans l'emploi intrathécal, en ce qui concerne du moins, les méningites.

Zusammenfassung

Über intrathekale Irritationen, verursacht durch Penicillin und physiologische Natriumchloridlösung

Untersuchungen wurden über die Wirkung von Penicillin und physiologischer Natriumchloridlösung angestellt, die intrathekal sechs Kindern verabreicht wurde.

10 000 bis 20 000 Penicillineinheiten, aufgelöst in 0.2—0.5 ccm physiologischer Kochsalzlösung oder distilliertem Wasser, brachten keine klinischen Symptome irgendwelcher Irritationen hervor. Nur ein Fall zeigte eine rektale Temperatur von 38.5° C. sechs Stunden nach der Injektion. In zwei Fällen von sechs konnte keine Vermehrung der Zellenanzahl in der Rückenmarksflüssig-

keit nach 24 Stunden konstatiert werden. Die übrigen wiesen keine sichere Veränderungen auf. Die höchste Zellenzahl war 80/ccm.

Natriumchlorid (5 ccm) brachte gewöhnlich eine Zunahme der Zellen hervor, die höchste Anzahl war 9 200/ccm in 24 Stunden. Bei jedem Fall konnte man eine Temperaturzunahme feststellen, die höchste war 40.2° C. (rektal). Bei drei Fällen stellte sich überdies eine vorübergehende Genickstarre ein und ein Patient klagte über Empfindlichkeit im ganzen Körper.

Penicillin, in 5 ccm Natriumchlorid aufgelöst, verursachte die gleiche Reaktion wie Chlornatrium allein.

50 000 Penicillineinheiten in 0.5 ccm Kochsalzlösung rief binnen zwei Stunden Bewusstlosigkeit hervor, heftige Zuckungen und Krämpfe im ganzen Körper. Die Temperatur stieg auf 40.0° C. Die Symptome liessen nach 24 Stunden nach.

10 000 Einheiten Streptomycin in 0.2 ccm Natriumchloridlösung erwies sich als wirkungslos.

Irritationsreaktionen, die von früheren Autoren dem Penicillin zuzuschreiben sind, werden erläutert und die Theorie angenommen, dass die Majorität dieser Irritationen wahrscheinlich dem Natriumchlorid, das als Lösungsmittel verwendet wurde, zuzuschreiben ist. Die Autoren meinen, dass Penicillin, gewissenhaft dosiert und verabreicht, keine gefährliche Substanz bei intrathekalem Gebrauch ist, wenigstens nicht bei Meningitis.

Sumario

Irritación intrarraquidea producida por la penicilina y solución de cloruro de sodio fisiologico

Se ha estudiado los efectos de la administración de la penicilina y de la solución fisiologica de cloruro de sodio por via intratecal en 6 niños.

10 000 a 20 000 unidades de penicilina disueltos en 0.2—0.5 ccm de suero fisiologico o agua destilada no produjeron ningun sintoma de irritación clinica. Solo un caso exibió una temperatura rectal de 38.5 C., 6 horas despues de la injección. En dos de los 6 casos no hubo a las 24 horas ningun aumento del numero de elementos celulares del liquido cefalorraquideo, el resto solo pre-

sento cantidades insignificantes. El numero mas alto abtenido fue de 80 por ccm.

El cloruro de sodio (5 ccm) produce regularmente un aumento de las celulas, el aumento mayor fue de 9 200 en las 24 horas. En todos se pudo observar un aumento de la temperatura alcanzando la mas alta a 40.2 C. (rectal). Tres casos presentaron ademas una rigidez de nuca pasajera, y uno de ellos presento dolores en todo el cuerpo.

Penicilina disuelta en 5 ccm de cloruro de sodio produjeron las mismas reacciones que el cloruro de sodio.

50 000 unidades de penicilina en 0.5 ccm de una solución salina, produjeron en dos horas, un estado de inconciencia, convulsiones y espasmos en todo el cuerpo. La temperatura se elevo a 40.0 C. Los sintomas retrocedieron en 24 horas.

10 000 unidades de Estreptomicina en 0.2 ccm de cloruro de sodio no produjeron ninguna respuesta.

Las reacciones de irritación descritas anteriormente por otros autores, como producidas por la penicilina son discutidas y se adelanta la teória de que la mayoria de ellas se deben probablemente al cloruro de sodio utilizado como disolvente. Los autores opinan que la penicilina correctamente dosificada y administrada, no constituye un agente peligroso para uso intrarraquideo, al menos en lo que a las meningitis se refiere.

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FROM THE SACHS CHILDREN'S HOSPITAL, STOCKHOLM.
CHIEF: J. HENNING MAGNUSSON, M.D.

The Treatment of Nephrosis with a High-Protein Diet and Casein Hydrolysate

by

GRETA HEDENSTRÖM

L.S., a boy aged five years, was admitted to the Sachs Children's Hospital on Nov. 5, 1947 (900/47). He had then been swollen for some days around the eyes and on the hands and external genitalia. During the preceding months he had shown no signs of infection. He had had no infectious diseases, had been vaccinated against variola at the age of six months, had always been strong and healthy, and his development had been normal.

On admission the patient's face was very oedematous, particularly around the eyes. There was slight oedema of the hands, the lower legs, and the scrotum. No ascites or hydrothorax. Weight 23.9 kg. Examination of the eyes revealed that the papillary margins were somewhat blurred but nevertheless within physiological limits.

The fauces were reddened. There was a harsh breath-sound over the base of the left lung. Temperature 38.4° C. Culture from the fauces showed the presence of Staph. aureus. Wassermann reaction in the blood negative. Blood determinations: chlorides 365 mg%, alkali reserve 59 vols. % CO_2, micro-sedimentation rate 45 mm/hr., hgl. 105 %, RBC 4.52 millions, WBC 9 600. The volume of urine was small, with a high specific gravity.

The serum calcium was later found to be between 8 and 8.4 mg%. X-ray examination of the skeleton three months after admission showed no decalcification. The remaining laboratory findings are assembled in Table 1 and Diagram 1.

The patient was given an ordinary diet, but the intake of fluids was restricted. Penicillin was administered in doses of 10 000 O.U. × 8 and continued until Nov. 19.

After twenty four hours the patient became much worse. The oedema became more massive and ascites and hydrothorax developed. Since violent vomiting made oral administration impossible, casein hydrolysate and glucose were given intravenously through a cannula starting on Nov. 7. 840 ml of a 3.3 solution of Aminosol with 5 % glucose were

Table

Date	Blood				
	Total Proteins %	Albumin %	Globulin %	Cholesterol %	Non-Protein Nitrogen mg%
Nov. 6	3.6	2	1.6	646	50
7	4	2	2	639	38
8	3.4	1.7	1.7	611	49
10	3.3	1.5	1.8		40
11	3				
12					35
13					
15	3.2			648	
19	3.2				48
24	3.1			847	61
28	3.7				45
Dec. 1					50
2					50
3					53
4				717	58
5					50
6					49
9					59
10	3.5	1.8	1.7	646	36
13					64
17					54
18	4			736	
23					
27					41
31					55
Jan. 2					46
8	4.8			779	
9					83
19					35
21	5.3	3.4	1.9	587	
29					44
31					33
Feb. 2	5.7	4	1.7	314	40
18	5.5			201	40
March 24	6.7	4.4	2.3	248	25
June 8					
Nov. 16	6.8	4.5	2.3	200	33

[1] Quantitatively 1 200 000 RBC per cm^3.

1

Urine		Blood Pressure mm Hg
Proteinuria	Sediment, Findings per Visual Field	
	A few RBC	115/90
2		120/90
4	2—4 RBC, a few hyaline cylinders	
2.5	A few RBC and hyaline cylinders	
2	» » » » WBC	
	» » »	
	» » »	
4	» » »	
2.5	» » »	110/80
2	» » » and some WBC	
	» » »	
	10—15 RBC, a few hyaline cylinders	
7	4—7 RBC, a few WBC, and granular and hyaline cylinders	110/75
	A few RBC, numerous hyaline cylinders. A few granular cylinders	
	A few RBC, numerous hyaline cylinders. A few granular cylinders	
	0—1 RBC	
	5—8 » and a few WBC and hyaline cylinders	
	0—2 »	
3	A few »	
	0—2 »	110/70
	0—3 »	
2	4—5 » a few hyaline cylinders	
5		
	A few RBC	
	5—6 »	
	A few RBC	
0.5	0—1 »	
	0—1 »	
	0—2 »	
0.04	2—4 » a few WBC	
	A few » and »	
	» » »	105/70
0.07	0	
0.07	A few RBC[1]	
—	A few RBC	
	0	
0	0	

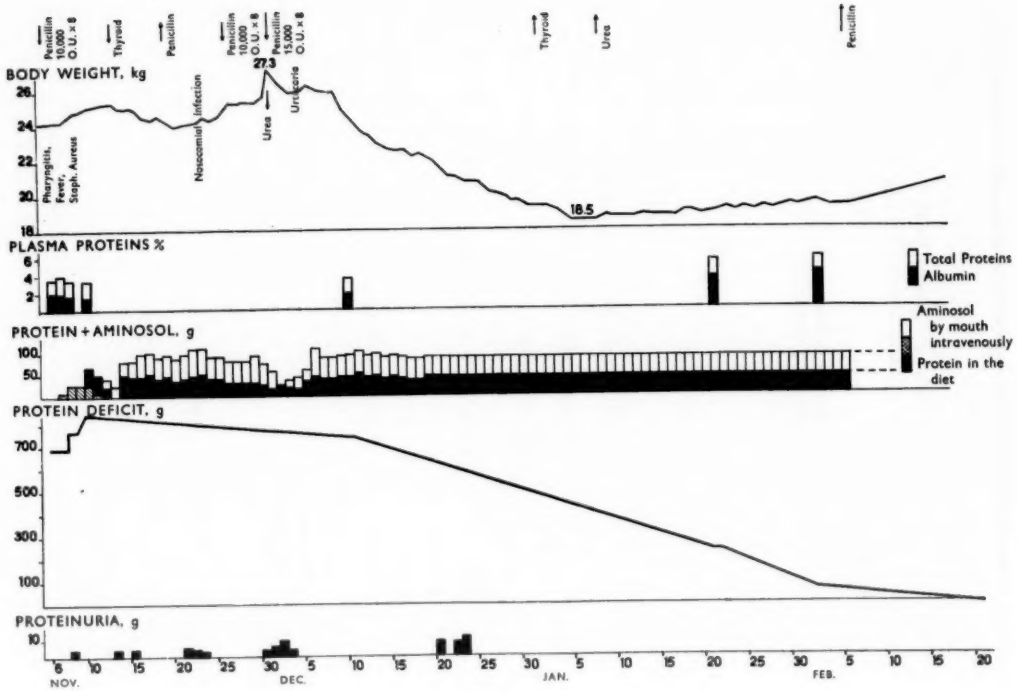
Penicillin 10,000 O.U. x 8
Thyroid
Penicillin
Penicillin 10,000 O.U. x 8
Penicillin 15,000 O.U. x 8
Thyroid
Urea
Penicillin
BODY WEIGHT, kg
27.3
18.5
Pharyngitis, Fever, Staph. Aureus
Nosocomial Infection
Urea
Urticaria
PLASMA PROTEINS %
Total Proteins
Albumin
PROTEIN + AMINOSOL, g
Aminosol by mouth intravenously
Protein in the diet
PROTEIN DEFICIT, g
PROTEINURIA, g
NOV.
DEC.
JAN.
FEB.

Diagram 1.

given per day. After scarcely five days the temperature fell and the vomiting ceased. The intravenous administration was stopped and the casein hydrolysate given by mouth in the form of Aminosol tablets. The patient was thenceforward kept on a high-protein, low-salt diet with restriction of fluids (300—400 ml per 24 hours). The intake of Aminosol was rapidly increased to approximately 2 g per kg of body weight and day. The patient was also given increasing doses of thyroid extract. His weight fell and the general condition improved somewhat.

About Nov. 20 his condition started once more to deteriorate considerably, with increasing oedema, ascites, and hydrothorax, and a decreased volume of urine. There was also vomiting. The non-protein nitrogen was around 50 mg% and the urinary sediment contained 10—15 red cells per visual field. The blood pressure was unaffected. In view of the nephritic complication, he was put on a low-protein diet beginning Nov. 26. The intake of Aminosol, however, was not changed. This exacerbation took place in immediate connection with the cessation of penicillin therapy and it continued and reached its maximum on Dec. 1, although penicillin was again given beginning Nov. 26. The patient then (Dec. 1) weighed 27.3 kg and his temperature was 39.4° C. Thereafter he was subfebrile until Dec. 4, when a very transient urticaria-like eruption occurred on the face. The dosage of penicillin was increased to 15 000 O.U. × 8 on Dec. 1 and urea, which had previously been avoided in view of the nephritic complication, was given.

Subsequently the oedema was reduced to some extent, the patient became more lively, and his appetite improved. The casein hydrolysate could soon be increased to 50 g per day in the form of Aminosol tablets and the protein in the diet to approximately 45 g per day. A definite improvement then ensued. There was an even, fairly slow increase in the plasma protein level with an increase of the albumin-globulin ratio. The oedema regressed and the proteinuria decreased successively. The improvement was also reflected in falling microsedimentation rates. The blood cholesterol likewise began gradually to decrease. When the patient was remitted to a convalescent home for children on Feb. 5, 1948, the total plasma proteins were 5.7 %, albumin 4 %, and the blood cholesterol 314 mg%. The previously very fluctuating non-protein nitrogen values had begun to be stabilized within normal limits and the urinary sediment contained only a few red blood cells. Tests with Esbach's reagent showed 0.2 ‰ proteinuria.

At follow-up examinations on Feb. 18, March 24, June 8, and Nov. 16, 1948, the patient showed no clinical abnormalities. Normal values were found for serum proteins, albumin, blood cholesterol, and non-protein nitrogen. On the first two occasions the sediment contained one or two red cells but at the last examination it was entirely free from pathological elements.

Discussion

The diagnosis that first suggests itself in this case is lipaemic nephrosis. There is much controversy regarding the relation of this disease to chronic glomerulonephritis but there are many indications that lipaemic nephrosis is a disease *sui generis*, particularly in childhood. Haematuria and retention of non-protein nitrogen may occur in an uncomplicated lipaemic nephrosis. The constant haematuria and the degree of non-protein nitrogen retention nevertheless make a nephritic complication very probable in our case (2, 16).

It is scarcely feasible to assess the possible aetiological significance of the Staph. aureus infection.

Owing to a morbilli incubation the day after his admission, the patient was given 5 ml of convalescent serum. A few weeks later he developed fever and a transient atypical eruption which was, however, probably of allergic character and caused by an ordinary nosocomial respiratory tract infection. The possibility that the morbilli infection had a favourable effect on the course of the lipaemic nephrosis need not therefore in this instance complicate the assessment of the therapeutic measures.

Because of the decreased resistance to infection, sulfa preparations or preferably penicillin are indispensable in the treatment of nephrosis. Diuretics, possibly urea in particular, can be beneficial.

Protein Deficit and Protein Therapy. — The decreased resistance to infection is presumably connected with the iontophoretically demonstrable decrease in the γ-globulin content of the plasma. This deficiency must in turn be referred to the proteinuria and the patient's general protein deficiency.

Similarly, the protein deficit, principally the hypoalbuminuria, must be the main cause of the oedema, even if the sodium chloride-water balance and the acid-base equilibrium are also of considerable importance (12, 15).

The protein deficiency thus stands out as the main feature in the clinical picture of lipaemic nephrosis. In the blood, it is in particular the plasma proteins that are affected. Anaemia is

seldom found and when it is present, it usually arises in connection with infections. Of the plasma proteins, it is in particular the albumin and the γ-globulin which decrease. The other plasma globulins, and to a still greater extent the fibrogen, often increase quantitatively. Qualitative changes in the different protein fractions also occur. A decrease in the amino acid picture in the blood has also been observed and this is accentuated in connection with nephrotic crises.

The albumin deficit in the blood is reflected in a protein deficit in the tissues. Elman and associates count on a mutual exchange of proteins between the blood and the tissues, a balance which can be expressed in a fairly constant numerical relation. In cases where the deficit is due to insufficient nutrition, the ratio of the albumin deficit in the blood to the protein deficit in the tissues is calculated as 1 : 30. Elman nevertheless makes a definite reservation in respect of a deficit caused by other factors and makes particular mention of nephrosis. In our patient the proteinuria can, however, be considered responsible only for a relatively small proportion of the albumin deficit in the plasma. It appears as though such a small leakage through the kidneys as is present here could displace the balance between the blood and the tissues only to a very slight extent. It therefore appears justifiable to make use of Elman's formula to obtain some idea of the patient's total protein deficit.

For the calculation, the plasma volume was assumed to be 1 000 ml (50 ml per kg) and the normal albumin content to be 4.2 g%. On admission to the hospital the albumin content was 2 % and there was thus a deficit of 22 g. The total protein deficit can be calculated from these figures as $660 + 22 = 682$ g.

The cause of the deficit has been sought not only in the proteinuria but also in disturbances in digestion or resorption or in the intermediary metabolism. Injury to the liver caused by a hypoalbuminuria can be of particular importance. The possibilities of affecting the disturbances in intermediary metabolism are small. The possibility which remains is to endeavour to compensate the protein deficit by the administration of plentiful proteins and amino acids.

It is known that one g of adequate protein per kg of body weight is sufficient to maintain the protein balance in a healthy adult. The administration of carbohydrates must also be sufficient, since otherwise the amino acids are metabolized to an abnormal extent in order to supply the need for energy. When there is protein deficiency, larger quantities of proteins must be given. Approximately 3 g per kg of body weight per day are usually considered suitable for nephrotic children. It has been established with the help of nitrogen balance investigations that quantities of proteins larger than 3.2 g per kg of ideal body weight per day do not bring about an increased utilization by the body but that instead the protein metabolism is damaged. The minimum is 2.5 g. Quantities between 2.5 and 3.2 g per kg of body weight per day do not constitute any risk in respect of renal function. Although a high-protein diet has been found to increase the clearance in nephrotic children, we must take into consideration the fact that an excessive administration of proteins can be unsuitable for a damaged kidney. The amounts given in the foregoing have been tested on five year old children, at which age 2.5—3 g of proteins per kg of body weight per day appear to be sufficient for the needs of growth but do not cause any increase in the plasma proteins or in the amino acid picture (8, 9).

Proteins and amino acids can be administered either by mouth or intravenously.

Plasma, concentrated low-salt human serum albumin, or amino acid mixtures can be given intravenously.

Plasma transfusions can be given in quantities of 200—300 ml daily, possibly over long periods. A good osmotic-diuretic effect can often be obtained and at times a very slight increase in the plasma proteins. A great disadvantage is that the protein administered must be broken down into amino acids before it can be utilized by the tissues and used for protein synthesis. Another drawback is that large quantities of salt and fluids are given to the body together with the plasma, the amount of protein being relatively small. This difficulty can be eliminated by using concentrated low-salt human serum albumin, which should also be of a certain nutritive value (4).

If the amino acid mixtures are given intravenously, the body is spared digestion of the protein and resorption of the amino acids and material immediately available for protein synthesis is offered to the tissues. The amount of fluid necessary for technical reasons is nevertheless fairly large. Considerable practical difficulties are also involved when patients must be nourished intravenously over such long periods as are necessary, nor is any direct osmotic effect achieved.

Administration of amino acids by mouth has been widely used in the treatment of nephrotic patients. Amigen has then been given most frequently. This is an enzyme-hydrolyzed casein derivate and contains amino acids and low-molecular polypeptides. In an American investigation the preparation was found to have no definite effect. Twenty g of Amigen daily were given to four children for three weeks. Their diet also contained 3 g of protein per kg and day. The Amigen was, however, given for too short a time and in too small quantities to allow any conclusions to be drawn from the report, particularly since the authors considered diet to be of very little importance in the treatment of nephrosis and it is probable that it was not controlled very strictly (12).

Satisfactory results have been obtained with concentrated low-salt human serum albumin. A four year old boy, to whom previously only 1.5 g of protein and amino acids per kg and day could be given owing to anorexia, was able — after his oedema had been reduced with serum albumin — to increase his intake to altogether 7 g per kg and day. The hypoalbuminuria was compensated by this means within two months (21).

By combining a high-protein diet with intravenous administration of amino acids, a total of 4.5—5 g per kg of body weight per day can be given and the nitrogen balance maintained. When in earlier investigations (8, 9) it was not possible to induce any increase in the albumin or the amino acids in the plasma in this way, the reason must have been that the duration of the experiment was too short.

The mortality in nephrotic crises has been reduced from 66 to 0 % by the intravenous injection of amino acids (8, 9).

The amino acid preparation used in our hospital has been

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Aminosol, which is produced by enzymatic hydrolysis of casein. The preparation for oral use consists of 76 % and that for intravenous use of 67 % free amino acids. The remainder is comprised of low-molecular dialyzable peptides (24). Five % glucose is added to the 3.3 per cent solution for intravenous use in order to increase the calories and thus facilitate the utilization of the amino acids in the synthesis of proteins. Aminosol has earlier been shown to be of great value in, among other things, the feeding of premature infants (19).

During the first nephrotic crisis in the case reported here, we were obliged to give Aminosol glucose intravenously. Since we did not wish to give too large quantities of fluid intravenously, the daily amount of proteins was too small for the needs of the patient (27.7 g). After a few days we were able to change to oral administration only. The amount in the diet was increased to between 40 and 50 g daily, approximately one-half of which consisted of animal proteins. In addition, approximately 50 g of Aminosol were given per day. The food was otherwise rich in carbohydrates and fairly poor in fats. After ten days the amount of proteins was reduced to 30 g per day, i.e. 1.5 g per kg, because of the nephritic complication. No change was made in the intake of Aminosol. After five days' protein restriction a fresh nephritic crisis occurred, but this subsided after three days without the necessity for intravenous nutrition. With all due regard to the nosocomial infection as the causative factor, it does not appear unreasonable to connect the culmination of the crisis with the decreased intake of proteins. The fact that the patient was nevertheless able to weather the crisis relatively well may conceivably have been due to the reserve of proteins that he had been able to accumulate during the preceding weeks, although the diuretic effect of the urea must also be taken into consideration.

After the second crisis was over, the intake of proteins and Aminosol could be increased rapidly and later be stabilized at 50 g of Aminosol and approximately 45 g of proteins in the diet per day, corresponding to 2.4 g of Aminosol and 2.2 g of proteins per kg of ideal body weight. This was continued unchanged for

seven weeks. After discharge from hospital the high-protein diet was maintained but the intake of Aminosol gradually terminated. The patient has never suffered any undesirable effects from these large amounts of proteins and Aminosol.

A continuous rise could be noted in the total proteins and in the albumin in the plasma. At the same time there was a reduction of the oedema with a loss in weight of altogether 8.8 kg, followed by a slow increase in weight as a sign of the rebuilding of the tissues. The proteinuria decreased rapidly and the blood cholesterol also began to fall slowly. The improvement was consistently gradual and did not occur suddenly as is usually characteristic of spontaneous remissions. Everything indicates that the greater part of the improvement must be ascribed to the plentiful intake of proteins and Aminosol. The patient was entirely free from symptoms at follow-up examinations on Feb. 18, March 24, June 6, and Nov. 16, 1948.

Summary

A five year old child suffering from nephrosis was treated continuously for seven weeks with a high-protein diet (2.2 g of proteins daily per kg of body weight) and large quantities of casein hydrolysate by mouth (2.4 g of Aminosol daily per kg). With this treatment the plasma protein values returned to normal and the child became clinically free from symptoms.

Résumé

Traitement de la néphrose par un régime riche en protéines et par la caséine hydrolysée

Un enfant de cinq ans souffrant de néphrose fut traité continuellement pendant 7 semaines par un régime riche en protéines (2.2 g de protéines par kg de son poids) et par absorption, per os, de grosses quantités de caséine hydrolysée (2.4 g d'Aminosol par kg quotidiennement). A la suite de ce traitement, la teneur du plasma en protéines redevint normale, et l'enfant fut debarrassé de tout symptôme clinique.

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Zusammenfassung

Die Behandlung von Nephrosis durch Hochproteindiät und Kaseinhydrolysat

Ein fünfjähriges Kind, das an Nephrosis litt, wurde 7 Wochen hindurch unausgesetzt mit einer Hochproteindiät (2.2 g Protein täglich für jedes Kilogramm des Körpergewichtes) behandelt und mit grossen Mengen Kaseinhydrolysat (2.4 g Aminosol täglich per Kilogramm) gefüttert. Bei dieser Behandlung wurde der Proteingehalt des Blutes wieder normal und das Kind wurde klinisch symptomfrei.

Sumario

Tratamiento de la nefrosis con una dieta de alto contenido proteico e hidrolizados de caseina

Una nefrosis en un niño de 5 años es tratado continuamente durante 7 semanas con una dieta de alto contenido proteico (2.2 g de proteinas por kg de peso) y con grandes cantidades de hidrolizados de caseina por via oral (2.4 g de Aminosol por dia y kg de peso). Con este tratamiento las proteinas del plasma volvieron a sus valores normales, y el niño quedo libre de sintomas clinicos.

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FROM THE PAEDIATRIC CLINIC OF KRONPRINSESSAN LOVISA'S CHILDREN'S HOSPITAL, STOCKHOLM.
CHIEF: PROF. A. LICHTENSTEIN.

Primary Pulmonary Vascular Sclerosis in Infancy

by

C.-G. HERDENSTAM

Degenerative changes in the vessel walls of the pulmonary artery can occur under many varying conditions and with different localizations. Sclerosis that has arisen in connection with a chronic pulmonary stasis — for example in mitral stenosis — or with some other chronic bronchopulmonary disease is often found in the larger branches of the artery. The smaller arteries of the lung can, however, also be affected in this form of pulmonary arteriosclerosis, which has long been known as secondary pulmonary sclerosis. In extremely rare cases, degenerative changes in the pulmonary vessels can appear without any associated primary cardiac or other pulmonary disease and unrelated to any general vascular disease. In these cases, usually designated collectively as primary or isolated pulmonary sclerosis, the vascular changes are most commonly localized only to the smallest arteries or to the arterioles. Owing to the increased strain on the right heart, both primary and secondary pulmonary sclerosis give rise to cor pulmonale.

The purpose of this paper is to review the essential points of the literature and to report a case of primary pulmonary vascular sclerosis occurring in a boy of 7 months. In view of the fact that this appears to be the first reported case of the condition in infancy, the presenting features and differential diagnosis will be discussed in detail.

Literature

Primary pulmonary sclerosis is an extremely uncommon disease. The last series of such cases was collected by BRILL and KRYGIER (8) in 1941 and comprised about 20 cases. Since then accounts

have been published of approximately 10 further cases, so that the total number of cases reported appears to be about 30. The minimum age was between 10 and 11 years and the maximum age 74 years.

According to BRENNER (7) it is only in exceptional cases of primary pulmonary sclerosis that the process is caused by an infection with an increase of cellular connective tissue in the intima and an inflammatory infiltration of cells in the media and the adventitia. BREDT (6), on the other hand, considers that the lesions are usually inflammatory and that they are comparable in pathology, histology, and genetics with pulmonary endarteritis. ROTHSCHILD and GOLDBLOOM (27) refer a case of primary pulmonary sclerosis described by them to this same type of endarteritic vascular affection. Irrespective of the histopathologic nature, the following factors have been suggested as causes of primary pulmonary sclerosis: a cryptogenetic infection (BRENNER (7)); allergy (ROTHSCHILD and GOLDBLOOM (27)); endocrine disturbances (SOKOLOFF and STEWART (30)); and a chemotrophic or chemotoxic injury (BREDT (6)).

The patients are usually admitted to hospital on the grounds of increasing symptoms of right heart failure, with dyspnoea, cyanosis, general venous stasis, and oedema. Dyspnoea is stated by BRENNER (7) and JERVELL (20), among others, to be considerably less severe in such cases than in other conditions of cardiac insufficiency. The conditions are the reverse as regards cyanosis, which in primary pulmonary sclerosis is often extremely severe and accompanied by polycythaemia. The slight degree of dyspnoea is presumably due to the absence of pulmonary stasis. Four of the 20 cases of primary pulmonary sclerosis assembled by BRILL and KRYGIER (8) suffered from angina pectoris. According to these authors, the precordial pain is accompanied by an acute coronary insufficiency on the basis of a greatly decreased blood flow to the left ventricle owing to the pulmonary sclerosis. BRENNER (7), however, interpreted the angina-like pains as so-called »hypercyanotic angina» produced by a lowered oxygen saturation in the arteries during periods of deep cyanosis, leading to chronic anoxaemia in the myocardium.

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As regards the microscopic findings, BRENNER (7) found in his 16 cases of primary pulmonary sclerosis that with one exception vascular lesions were localized to the pulmonary circulation only. The smallest branches of the pulmonary artery were usually most severely affected, with proliferations containing few cells in the intima. These compressed the lumen but often failed to obliterate it. In BRENNER's material a moderate atherosclerosis in the large arteries of the lung was the only vascular lesion in 7 cases of 16. In all the cases the right heart was enlarged and in many instances there was marked hypertrophy and dilatation of the right ventricle, whereas the left heart was on the small side. The degenerative changes described in the myocardium were usually moderate.

Diagnosis. The x-ray or fluoroscopic examination reveals right-sided cardiac hypertrophy, which is an important feature in the syndrome of pulmonary vascular sclerosis (SOKOLOFF and STEWART (30), BRENNER (7), JERVELL (20), BRILL and KRYGIER (8), and JENSSEN (19)). In addition to the right-sided cardiac hypertrophy, more or less pronounced prominence of the pulmonary conus is usually seen on the radiogram. The presence of clear, poorly vascularized pulmonary fields has also been observed by BRILL and KRYGIER (8) and JERVELL (20). The electrocardiographic changes in a cor pulmonale caused by pulmonary sclerosis are usually considered to consist of a right axis deviation, enlarged P waves, and possibly inverted T waves and depressed S-T segments in Lead II—III (BRENNER (7), JERVELL (20), SMEDSRUD (29), BRILL and KRYGIER (8), JENSSEN (19), and ØRNING (34)). The changes in the S-T segments and T waves are not, according to BÜCHNER (10) and SMEDSRUD (29), the expression of the hypertrophy as such, but of the relative, right-sided coronary insufficiency caused by it. In a hypertrophied heart musculature with a constantly increasing area of supply for the individual capillaries, a maladjustment between the oxygen requirement and the supply of blood gradually takes place. Since the taking up of oxygen is made more difficult by the hypertrophied myofibris, this contributes to the occurrence of chronic coronary insufficiency.

Among the other results of examination given in a number of case histories of primary pulmonary sclerosis one may mention an accentuated second pulmonary sound, a systolic murmur, and, as a rule, distinct polycythaemia accompanying the cyanosis. In a case published by ROTHSCHILD and GOLDBLOOM (27) it was also found that the arterial oxygen saturation was only 50 %.

Case Report

J.E.A. (No. 1045/1948), a boy aged 7 months, b. May 12, 1948. No cardiac or pulmonary diseases in the hereditary history. Social conditions good. The mother, born in 1917, was healthy during pregnancy with the exception of a slight respiratory tract infection in the early stage. The delivery was normal and at full term. The child weighed 3 340 g at birth. The neonatal period was normal. At the age of 2 weeks the infant began to show signs of fatigue and dyspnoea during feeding. There was also slight dyspepsia. Although the feeding difficulty increased and dyspepsia continued, the child gained weight satisfactorily until the age of 7 weeks, when the weight began to remain stationary. A cardiac murmur was then found and the mother was informed that the child had a slight congenital cardiac malformation. The child's subjective symptoms during feeding became increasingly severe. He became more easily fatigued, vomited frequently, and was at times distinctly dyspnoeic. From the age of 11—12 weeks, at intervals of approximately 1 week, there were days on which he absolutely refused to take the breast. He had attacks of violent and intense screaming during which he threw his arms about and assumed an opisthotonic position in bed. During these attacks of screaming, which usually lasted for about an hour, he became very dyspnoeic, his colour was greyish and cyanotic, and he was clammy, with cold sweat over his whole body. His eyes were staring and fixed and he gave the impression of being in extreme pain. Because of these attacks he was first admitted to the hospital at Västerås and on Sept. 20 to Kronprinsessan Lovisa's Children's Hospital in Stockholm.

Condition at Age of 19 Weeks

General. Small, miserable-looking boy. Weight 4 070 g (= 2.5 kg underweight). Height 59 cm. No cyanosis or dyspnoea. No oedema. Skin pale and veins clearly visible. No finger clubbing nor hour-glass nails. No signs of rickets. Temperature 36.7° C.

Heart. No precordial bulge. Slight systolic thrill over lower part. Apex beat not easily palpable. No pathological pulsations. Fairly harsh systolic murmur with maximum point in fifth left intercostal space over

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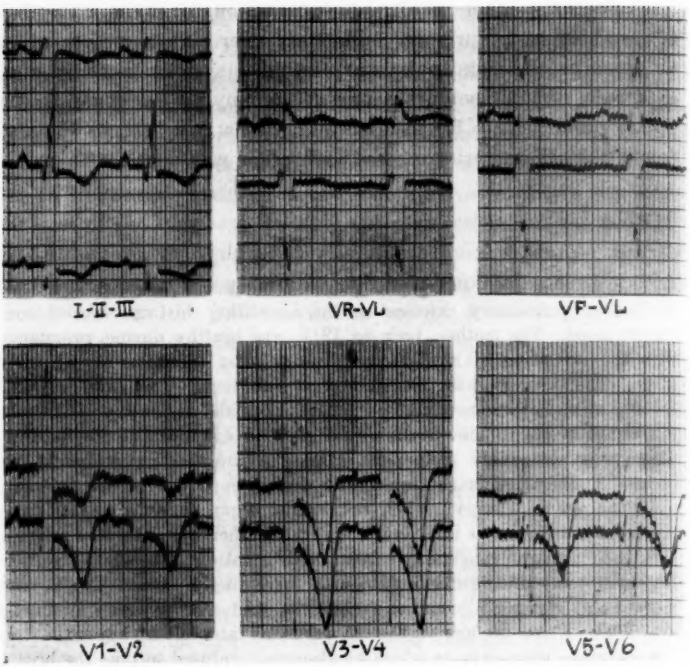

Fig. 1. E.C.G. at age of 19 weeks.

Standard leads: I—III. Unipolar precordial leads: V1—V6. Unipolar extremity leads: VR—VL—VF.

lower medial part of precordium. Accentuated second pulmonary sound. Regular, rapid rhythm. Blood pressure: 95 systolic.

Lungs. Vesicular breathing, no adventitious sounds nor diminution.

Abdomen. Soft; no tenderness. Liver palpable immediately below right costal margin. Spleen not palpable.

Laboratory Findings. Hgb. 12.2 g = 80 %; RBC 4.32 mill.; WBC 7 200. Differential blood count: staff cells 7 %, segm. 24 %, lymphoc. 66 %, monoc. 3 %. Microsed. rate: 3 mm/hr. No sugar or albumin in urine. Urinary sediment: N.A.D. Neotuberculin negative. Mother's Wassermann and Kahn negative.

ECG (standard leads and unipolar precordial and extremity leads according to F. Wilson's method). Rate rapid (131—154/min). Rhythm

regular. PQ interval = 0.11 sec. Right axis deviation (angle of electric mean axis = + 127°). Marked right ventricular hypertrophy and moderate auricular enlargement. Heart in horizontal position, rotated clockwise around its long axis (seen from apex according to Goldberger). Signs of extensive, severe myocardial damage with depressed S-T segments in most leads and inverted T waves in all leads (max. 2.9 mV in Lead V4). See Fig. 1.

X-ray Examination of Heart and Lungs (Dr. S. Eek of Rikshospitalet, Oslo). Heart considerably enlarged and of pathological shape. Major part in left half of thorax, 2.2 cm on right and 6.0 cm on left of medial line in AP position. Cardiothoracic index 0.68 and volume 113 ml, or 470 ml per square meter body surface (Fig. 2). Vascular markings in hilus and pulmonary fields small. Pulmonary fields therefore apparently clear, leading to suspicion of inadequate blood flow in pulmonary circulation.

The immediate impression given by the case on this first examination was that a pronounced left-sided enlargement both of the auricle and the ventricle was present. In view of the short, extremely convex posterior left contour of the heart in the left oblique and lateral projections (Figs. 2 C and 2 D), which refer to the left ventricle, it was nevertheless suspected that the appearance on radiography could be occasioned by a gross enlargement of the right ventricle. This would then have displaced the left ventricle increasingly backwards and upwards and finally to the right, thereby rotating the left ventricle counterclockwise and causing a displacement of the oesophagus. This assumption was confirmed at the later x-ray examination at the age of 27 weeks, when the interventricular groove was visible and the degree of convexity of the left ventricle was more distinctly shown on the lateral picture (Fig. 3 D).

Radiological Diagnosis. Extremely enlarged, presumably transverselying heart, with gross enlargement of the right side. Poorly vascularized, clear pulmonary fields.

Angiocardiography (performed Nov. 22 at Norrtull Hospital by Drs. Wegelius and Lind using an apparatus for direct photography with rapid changing of the casette, in this case permitting a rate of 7 exposures per second). Heart considerably enlarged. Contrast flowed in normal way through right auricle, which was appreciably enlarged, to right ventricle, also enlarged. Pulmonary conus, pulmonary artery, and main branches of latter satisfactorily filled with contrast.

Clinical Diagnosis. Anomaly of coronary vessels. The suspicion of an abnormal origin of the left coronary artery from the pulmonary artery appeared the most plausible in view of the ECG evidence of severe myocardial damage, the first supposition of a left-sided cardiac enlargement, and the case history, typical of coronary anomaly.

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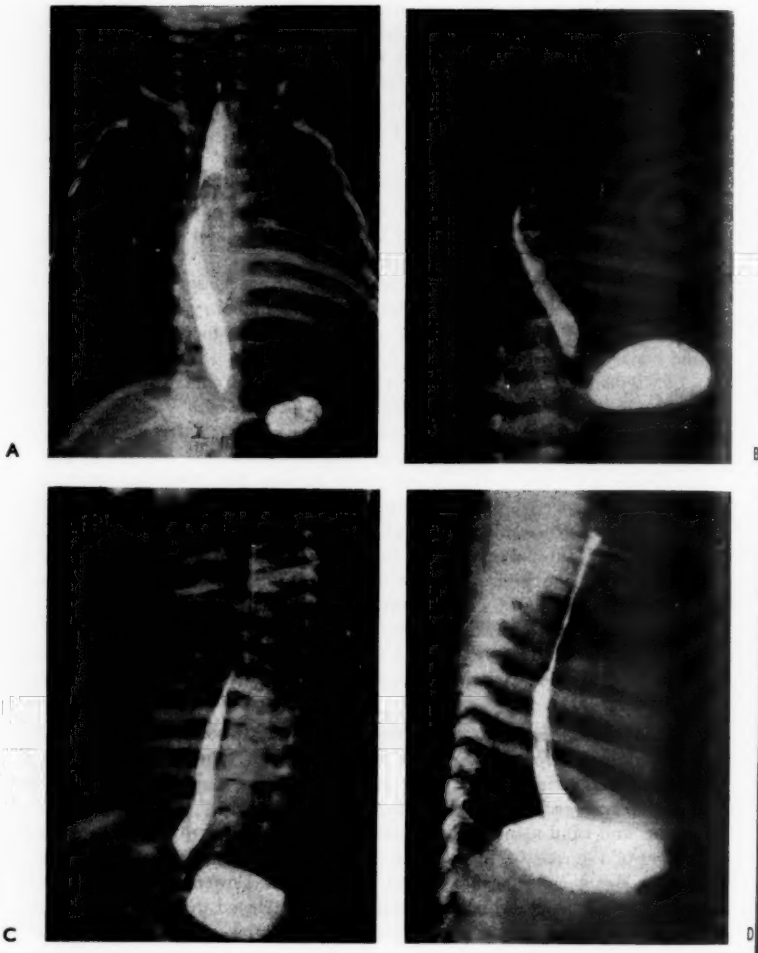

Fig. 2. Radiological examination of heart at age of 19 weeks, with opaque substance in oesophagus.

A = anterior—posterior position. B = right anterior—oblique position. C = left anterior—oblique position. D = left lateral position.

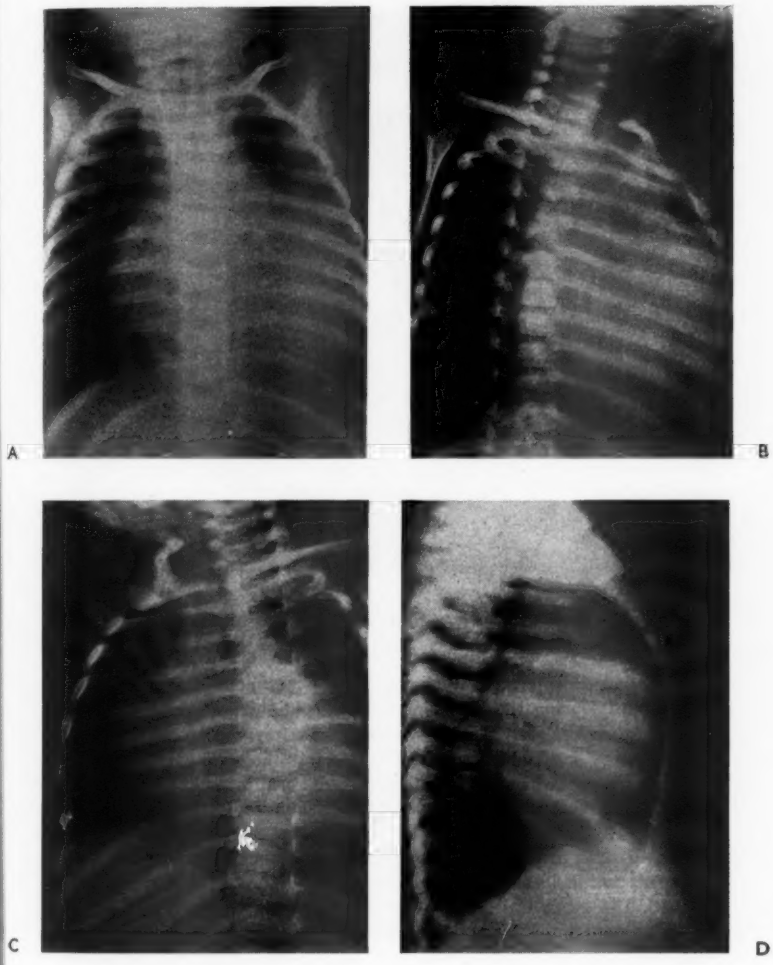

Fig. 3. Radiological examination of heart at age of 27 weeks; no opaque substance in oesophagus.

A = anterior—posterior position. B = right anterior—oblique position.
C = left anterior—oblique position. D = left lateral position.

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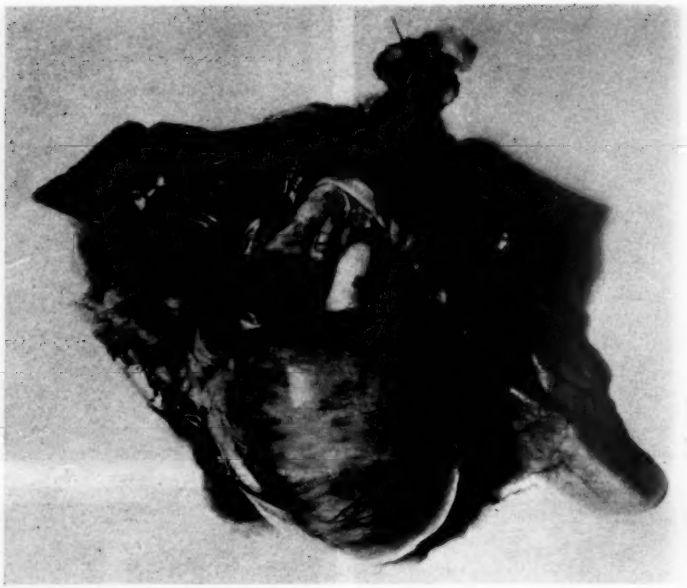

Fig. 4. Photograph of heart and lungs.

Treatment. Intermittent oxygen therapy at home was prescribed.

Course. During the following 2 months the child's condition was on the whole unchanged. His weight remained fairly constant at 4 200 g, the difficulty in feeding was the same, and the temperature remained normal. The attacks, which still occurred at approximately weekly intervals, nevertheless became considerably less severe with the oxygen therapy. In the middle of Dec. a respiratory tract infection developed at home. Since a series of unusually severe attacks also occurred, he was admitted to the local hospital in Västerås, where he died suddenly on Dec. 13, 1948.

Examination of Heart and Lungs (Drs. Bergstrand and Ohlsson). The macroscopic examination was made according to Bergstrand's method (4) for the study of the coronary arteries.

The heart was considerably enlarged and weighed 110 g, the normal weight at this age being approximately 35 g (Fig. 4). The right ventricle was moderately dilated and extremely hypertrophic with coarse and much thickened trabeculae. The wall of the right ventricle was just

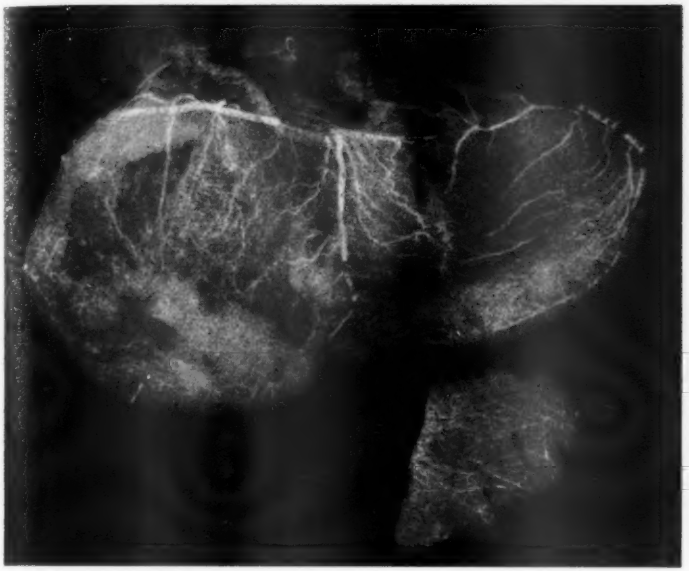

Fig. 5. Radiograph of heart with injected coronary arteries according to Bergstrand's method (4).

over 1 cm thick and throughout almost twice as thick as the left. There was considerable dilatation of the right auricle, which was at least twice the size of the left. The interventricular septum was of ordinary thickness, with no defects. There were no definite changes in the left auricle and ventricle. Both the mitral and the tricuspid valves were slightly thickened in places and oedematous, but with no endocardial deposits. The aortic and pulmonary valves were normal. No noteworthy changes were visible in the large vessels. The coronary arteries had their origin in the normal manner from the left and right sinus of Valsalva. The course of the coronary arteries was normal. They were also of normal width and well filled with the contrast material and could therefore be followed in their small peripheral branches. The number of these branches appeared to be decreased in the anterior lower part of the right ventricle (Fig. 5). The myocardium, which was very markedly thickened, was somewhat uneven in colour and pale on the cut surface and had streaks of distinctly greyish colour. No apparent evidence of either old

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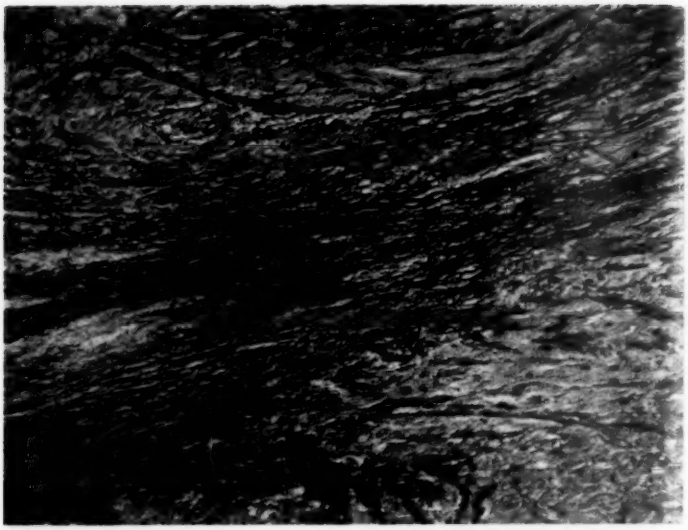

Fig. 6. Section from apical part of anterior wall of right ventricle. Foci consisting of relatively dense and collagenous connective tissue.

Staining: v. Gieson. Magnification: 75×. Naphthol green filter.

or recent infarction was found in the right or left ventricular wall or in the septum. The lungs were normally air-filled and evinced no gross changes.

Microscopic Examination. Sections from various parts of the right and left ventricles, the interventricular septum, the right and left auricles, the interauricular septum, the mitral and tricuspid valves, and from all the lobes of the lungs were examined. Staining: v. Gieson, Scharlach, and Weigert's elastin.

The wall of the entire right ventricle showed a diffuse or patchy fibrosis of varying intensity. In parts this was of the nature of a diffuse increase in the connective tissue between the muscle fibers, which at these sites were often narrower than normal and with granular fragmentation, a lack of cross-striation, and more or less pycnotic, deformed vesicular nuclei. In large areas the fibrosis consisted of irregular patches of continuous collagenous connective tissue (Fig. 6). In places the patches of connective tissue were composed of loose connective tissue, poor in collagen, in which islets of necrosing, hyaline, or granular residues of

Fig. 7. Section from anterior papillary muscle in left ventricle. In myocardium a focus consisting mainly of loose connective tissue, in which structureless remains of muscle fibers are seen.

Staining: v. Gieson. Magnification: 300×. Naphthol green filter.

muscle fibers could be seen, with differences in depth of staining and no nuclear staining (Fig. 7). A few lymphocytes, single plasma cells, and polynuclear leukocytes as well as a number of small vessels could also be observed in these foci. The larger vessels in the myocardium were fairly wide, filled with the contrast material and showed no definite pathological changes.

The myocardial lesions were most apparent in the inner parts of the ventricular wall, particularly in the trabeculae, where large continuous foci of connective tissue were seen. In the more central parts of the wall they were of the nature of a diffuse interstitial increase in connective tissue. Only slight myocardial changes were found in the outer, subpericardial parts. The myocardial lesions were as a rule not localized to the perivascular regions, which often consisted of almost normal muscle fibers. The lesions were most extensive and severe in the anterior lower part of the right ventricle and around the apex. In the left ventricle there were similar lesions in the papillary muscles, particularly

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Fig. 8. Section from upper lobe of right lung with obliterated small arteries and large artery showing muscular hypertrophy of wall.

Staining: v. Gieson. Magnification: 75×. Naphthol green filter.

in the anterior, whereas the rest of the ventricular wall showed only suggestions of similar changes. No definite changes were seen in the endocardium. No very pronounced changes were visible in the walls of the auricles, although here the endocardium appeared to be somewhat sclerosed. Fairly pronounced and oedematous swelling was visible at the margins of the tricuspid valves as well as an increase of nuclei at some sites with evidence of a fibrinoid reaction. There was no inflammatory infiltration of cells. The mitral valves were also somewhat oedematous with fibrinoid margins.

There was considerable hyperaemia in the lungs, particularly in the left lower lobe. The bronchial lumina showed much desquamated epithelium as well as a few polynuclear leukocytes. Scattered in the peribronchial connective tissues there were infiltrations of lymphocytes, plasma cells and leukocytes. In the alveoli of the lungs there were foci of inflammatory cell elements containing thin serous fluid with little fibrin. In all the lobes, particularly in the upper lobes, the small arteries showed considerable changes with proliferation, mainly of the intima, thus most frequently causing total obliteration of the lumen

(Fig. 8). Only 1 or 2 round cells could be seen in the adventitia of the vessels, which was often somewhat sclerosed. In some of the vessels with proliferations in the intima, a fairly sparse globular substance, with evidence of fat-staining reaction, was found. The affected vessels were often very near the bronchi. A slight thickening of the intima and a moderate muscular hypertrophy were also found in some places in the larger arteries.

Postmortem Diagnosis. Pulmonary sclerosis with hypertrophy and severe degeneration of the right ventricle of the heart. Bronchitis and acute bronchopneumonia.

Epicrisis. The patient was a boy aged 7 months who after a normal neonatal period showed increasing difficulties in breast feeding and periodic attacks of collapse with severe pain. The clinical examination, which included ECG and x-ray examinations, revealed pronounced cor pulmonale, i.e. considerable hypertrophy of the right ventricle with signs of severe myocardial damage, together with poorly vascularized, clear pulmonary fields. This condition was found at postmortem examination to be pathogenetically associated with pulmonary sclerosis. In view of the absence of any other heart disease or of another bronchopulmonary process, this pulmonary sclerosis can therefore be regarded as primary.

Comments

The pathogenesis of the vascular lesions in the case reported here appeared to be of non-inflammatory nature. According to BRENNER (7) it would thus be typical of the greater part of his own series. It appears plausible to interpret — as does Brenner — the pulmonary sclerosis and the right-sided cardiac hypertrophy as pathological occurrences with a common unknown genesis. However, the possibility might be considered that the origin of the vascular lesions could in some way be associated with the slight maternal infection during the early stage of pregnancy.

With regard to the symptomatology the nursing difficulty was here in the foreground. This might possibly be explained by the great displacement of the oesophagus. In addition, there were attacks of collapse with severe pain of exactly the same nature as the attacks described by SOLOFF (31) and by EIDLOW and

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MACKENZIE (12), among others, in coronary anomalies with severe, degenerative lesions in the myocardium, attacks which were compared with the acute coronary attacks in adults. The attacks of pain in the patient described here would thus represent the very earliest stage of angina pectoris arising on the grounds both of the decreased blood flow to the left heart and of the relative coronary insufficiency associated with the hypertrophy.

The diagnosis in the present case could be made only after the histopathological examination of the heart and lungs. The incorrect clinical diagnosis of an anomaly of the coronary vessels was due mainly to the difficulties of diagnosing the right-sided cardiac hypertrophy at the x-ray examination. According to EEK (11), a careful study of the degree of convexity of the left ventricle is of prime importance for making a radiological diagnosis in cases when the interventricular groove is not visible (Figs. 2 C and 2 D). In the case reported here, the ECG changes were extremely significant. The right deviation of the electric mean axis could be related to a marked right-sided ventricular hypertrophy in a transversely-lying heart. In addition to the typical P pulmonale, there was a sign of severe myocardial damage in the form of a very depressed S-T segment and deeply inverted T waves. The latter changes were very prominent, compared with the morbus caeruleus material published by HERDENSTAM and MANNHEIMER (16), probably due to the fact that the hypertrophy in these cases is seldom as pronounced.

The degenerative changes described in the myocardium were very prominent and it has not been possible to find any case of primary pulmonary sclerosis with the extensive fibrosis encountered in the case reported here. A similar extensive fibrosis of the myocardium as the result of chronic coronary insufficiency in severe cardiac hypertrophy was, however, reported by STIASSNY (32). His patient was a boy aged 4 days with marked left-sided hypertrophy caused by a congenital malformation of the aortic valves.

The differential diagnosis appears to present different clinical aspects at different ages. In adults and older children, the main task is to exclude a cor pulmonale that is secondary to some

chronic bronchopulmonary disease such as emphysema, bronchiectasis, pneumoconiosis, chronic fibrous pulmonary tuberculosis, bronchial asthma, Boeck-Schaumann sarcoidosis, or the like. In early infancy the main problem is to differentiate from congenital heart disease. In view of the clear, poorly vascularized pulmonary fields and the enlargement of the right heart, tetralogy of Fallot or isolated pulmonary stenosis are the major problems. These congenital heart malformations can, however, usually be diagnosed with the help of angiocardiography and heart catheterization.

In view of the severe ECG changes and the dramatic case history in the present case, 4 further conditions appear worth mentioning.

1. There may be an abnormal origin of the left coronary artery from the pulmonary artery. This results in the left ventricular wall being supplied with venous blood mainly in its anterior parts, corresponding to the area of extent of the left coronary artery. In this way chronic anoxaemia arises in this part of the heart, leading to degenerative changes in the form of a patchy necrosis and fibrosis in the myocardium and often to an excessive dilatation of the ventricle wall (HEIDLOFF (15), HAFERKORN (14), BARNARD (1), and BENESOVÁ (2)). In a number of such cases the symptoms were similar to those reported here. After a normal neonatal period, the child suffered from attacks with collapse during nursing, often accompanied by severe pain. The electrocardiograms revealed severe myocardial damage and the x-ray examinations considerable enlargement of the left ventricle. BLAND, WHITE, and GARLAND (5) are of the opinion that an anomaly of the coronary arteries should be suspected in an infant when enlargement of the heart is found radiologically, the ECG reveals signs of myocardial infarction, and anginal attacks occur. SOLOFF (31) and EIDLOW and MACKENZIE (12) consider that a diagnosis intra vitam should be possible on approximately the same grounds. The similar ECG changes and the coronary attacks in the case of pulmonary sclerosis reported here nevertheless indicate that a special diagnosis on this ground alone is extremely difficult.

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2. So-called infantile infarction on the basis of a coronary thrombosis is a possibility. Such a case, in which the patient was a 4 month old girl, was described by RAMSAY and CRUMRINE (26). The thrombosis, which was assumed to be caused by a bacterial embolus, had occluded the left coronary artery, thus causing an infarction in the wall of the left ventricle.

3. An infantile infarction can be present, arising through an occlusion of the coronary arteries in a general disease of the vascular walls. According to STRYKER (33) this is never of arteriosclerotic nature in the case of infants but it is usually a question of a calcification of the media with a fibroblastic proliferation of the intima. STRYKER (33) reported about 10 such cases. In these instances the coronary arteries can stand out as thickened, solid, tortuous cords on the surface of the heart (MC MICHAEL (24), HUGHES and PERRY (17), and BRYANT and WHITE (9)). An extensive, fairly severe sclerosis of the media of Mönckeberg's type in infants with pronounced lesions in the coronary arteries was also described by IFF (18) and KISSANE and FIDLER (22). In the last-mentioned case, a 3 day old boy, the electrocardiogram showed an infarction in the anterior wall with raised S-T segments and inverted T waves in lead I.

The pathological findings in this case of primary pulmonary sclerosis exclude the possibility that it could belong to any of these 3 groups.

4. Finally, the question of a cryptogenic, isolated infantile myocarditis arises, i.e. corresponding to Fiedler's myocarditis in adults. This disease, which can affect a formerly healthy infant, is characterized — according to KELLER (21), BERGMAN (3), and LIND and HULTQUIST (23) — by difficulty in feeding, with refusal of food, vomiting, and constitutional disturbances with dyspnoea, pallor, and cyanosis. The course is usually very rapid, with a fatal outcome within a few weeks. Radiological examination reveals an enlarged heart and the electrocardiogram shows mainly changes in the S-T segments and T waves. Microscopic examination of the myocardium reveals both degenerative lesions, often in the form of a subendocardial fibrosis, and a lymphocytic or polynuclear cellular infiltration. The latter finding was, how-

ever, lacking in a case described by FROBOESE (13). His patient was a girl of 6 months in whom the fibrotic foci in the myocardium were interpreted as the expression of a congenital myocarditis. In the case reported here, the protracted course, the persistently normal temperature, and the acellular myocardial lesions speak against an infantile myocarditis.

Summary

The literature on primary pulmonary vascular sclerosis is reviewed and a case of this disease in a boy of 7 months described. This appears to be the first case reported in infancy. The symptomatology is characterized by a failure to gain weight, caused by feeding difficulty, and attacks resembling angina pectoris which were earlier considered pathognomonic of an anomaly of the coronary arteries in conjunction with an enlargement of the left ventricle.

Radiological examination revealed clear, poorly vascularized pulmonary fields and a gross enlargement of the heart. This was first considered to be caused by the left ventricle but was later found, when the interventricular groove was demonstrated, to be due to a marked enlargement of the right heart. The electrocardiogram revealed signs of severe myocardial damage, mainly of the type of an infarction, and pronounced right-sided cardiac hypertrophy. The diagnosis was made on the basis of the microscopic examination of the heart and lungs.

Résumé

On a passé en revue les ouvrages concernant la sclérose vasculaire pulmonaire primaire et on décrit un cas de cette maladie chez un petit garçon de sept mois. Ce cas semble être le premier rapporté chez des infants. La symptomatologie est caractérisée par l'absence d'augmentation de poids, causée par des difficultés d'alimentation, et des attaques ressemblant à l'angine de poitrine, qui étaient auparavant considérées comme pathognomoniques d'une anomalie des artères coronaires conjointement à une dilatation du ventricule gauche.

Un examen radiologique a révélé la présence de champs pul-

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monaires nets peu vascularisés et une forte agrandissement du coeur. On a d'abord considéré que cela était causé par le ventricule gauche, mais on a découvert ensuite, après avoir démontré le sillon interventriculaire, que le fait était dû au ventricule droit. L'électrocardiogramme a révélé de graves signes de lésion myocardiale, principalement du type d'une infarction, et une hypertrophie cardiaque prononcée du côté droit. Le diagnostic a été établi sur la base d'un examen microscopique de coeur et des poumons.

Zusammenfassung

Die Literatur über die primäre Sklerose der Lungenschlagader wird besprochen und ein Fall von dieser Krankheit bei einem Jungen von sieben Monaten beschrieben. Dieser scheint der erst beschriebene Fall bei Kindheit zu sein. Die Symptomatologie wird gekennzeichnet von mangelnder Zunahme an Gewicht, hervorgerufen von Schwierigkeiten mit der Zusichnahme der Muttermilch und von Anfällen ähnlich wie bei der Angina pectoris. Die letzteren wurden früher als pathognomonisch für eine Anomalie der Koronararterien in Verbindung mit einer Vergrösserung der linken Herzkammer betrachtet.

Die Röntgenuntersuchung stellte klare, schlecht durchblutete Lungenfelder und eine starke Herzvergrösserung fest. Anfangs nahm man an, dass diese von der linken Herzkammer hervorgerufen worden sei, aber es stellte sich später, als die interventrikuläre Furche gezeigt wurde, heraus, dass es auf eine Vergrösserung der rechten Herzkammer zurückzuführen sei. Das Elektrokardiogramm zeigte ernste Anzeichen von Myokardschaden wie bei einem Herzinfarkt und ausgesprochene rechtsseitige Kammerhypertrophie. Die Diagnose wurde gestellt auf Grund der mikroskopischen Untersuchung von Herz und Lungen.

Sumario

Se estudia la literatura médica sobre esclerosis vascular pulmonar primaria y se describe un caso de esta enfermedad en un niño de 7 meses. Parece que éste es el primer caso infantil de dicha enfermedad sobre el cual se ha informado. La sintomato-

logía se caracteriza por la falta de aumento de peso, causada por dificultades de nutrición, y por ataques parecidos a angina pectoral, la cual anteriormente fué considerada como patognomónica de una anomalía de las arterias coronarias en combinación con un aumento del ventrículo izquierdo.

El examen radiológico descubrió regiones definidas deficientemente vascularizadas y un gran agrandamiento del corazón. Primero se creyó que esto era causado por el ventrículo izquierdo, pero posteriormente se vió, después de haber sido estudiado el surco interventricular, que la causa era un marcado agrandamiento de la parte derecha del corazón. El electrocardiograma mostró serias señales de daños miocardíacos, principalmente del tipo de infartación, y una hipertrofia cardíaca, sobre todo en la parte derecha del corazón. El diagnóstico se hizo a base del examen microscópico del corazón y de los pulmones.

I wish to express my sincere thanks to Dr. A. Normark, who sent the case from the Västerås Hospital, and to Drs. S. Eek, S. Ohlsson, and C. G. Bergstrand, who were kind enough to assist in the investigation. My thanks are also due to Professor F. Henschen, with whom I was able to discuss the problems, and to Dr. E. Mannheimer, who gave me very valuable advice in the preparation and publication of the present study.

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Some Aspects of the Problem of Prematurity

by

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The premature infant is only one of many topics in paediatrics our knowledge of which has been enriched by the studies of Lichtenstein. It is a privilege and a pleasure to discuss some aspects of this problem in a volume dedicated to him.

In a half century in which unprecedented strides have been made in reducing infant deaths, the mortality from prematurity has lagged behind the general downward trend, with the result that prematurity is now our major cause of infant mortality. In New York City in 1889 only 6 % of deaths under 1 year were attributed to prematurity, whereas in 1946 the figure was 42 %. This picture is typical of the United States as a whole and of many other countries. The situation is not altogether a discouraging one, for the absolute mortality among prematures has been steadily, if slowly, declining during this period and the premature born today has twice the chance of survival that he had at the turn of the century. It is the more rapid elimination of other causes of death that tends to focus our attention upon him.

In formulating a further attack on premature mortality we may consider: (1) measures that have been successful in reducing mortality to date, (2) what we may expect from their more intensive application, and finally (3) the possibility of new approaches to the problem.

It is difficult to evaluate individually the different factors that have contributed to the reduction of premature mortality to date. Public health measures and better obstetrical and paediatric techniques have combined to bring this about.

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Among the public health measures that have been brought to bear in the United States may be mentioned the development of medical centers furnishing experienced medical and nursing personnel, the development of special transport facilities, such as heated ambulances, to bring infants often long distances to these centers, the development of follow-up services, and, finally, a variety of educational efforts on the part of health agencies designed to alert the profession and the public to the importance of the problem.

Effective obstetrical measures include improved and more widespread prenatal care, the gradual replacement of midwives by physicians and of home deliveries by hospital deliveries, better diet during pregnancy, better treatment of complications of pregnancy, avoidance of harmful narcotics and anaesthetics, a reduction in obstetrical trauma, and better resuscitation procedures. The effect of prenatal vitamin K administration is disputed. Undoubtedly the obstetrician today is presenting the paediatrician with fewer premature babies and with babies in reasonably good condition who in former years would have been damaged, but he is also presenting us with damaged babies who formerly would have been dead. It is not clear that the character of the paediatric case load of premature babies has been substantially altered.

Paediatric progress has consisted in measures designed to overcome the more important handicaps of prematurity — notably, improved mechanical devices for regulating the temperature and the humidity of the environment and for the administration of oxygen. Better isolation techniques, such as the isolation incubator, have reduced the hazard of infection to a minimum and chemotherapy is available to combat those that do develop. The elimination of clothing in incubators permits exercise and better expansion of the lungs. And, finally, we have made progress in nutrition — recognizing a need for more protein, vitamin C, and vitamin D in the diet. Vitamin K given postnatally has doubtless played a part in reducing haemorrhage.

It is to be expected that the wider application of these techniques will reduce premature mortality, presumably to figures such as obtain in our leading medical centers today. Research

along current lines may clarify some questions that are now contentious and lead to policies which will produce some further improvement. It is the purpose of the present communication to point out, however, that we are approaching a limit in our current efforts to reduce premature mortality. Much of our current research is directed towards problems which are now virtually solved and it behooves us to orient our work and our thinking toward the one major problem in premature mortality which today is receiving almost no attention.

Students of prematurity are today still largely concerned with the three traditional major difficulties of the premature infant — regulation of the physical and chemical environment, prevention of infection, and feeding. Beyond a doubt there are still problems in all these fields. There are better gadgets to be designed, optimum concentration of moisture and oxygen to be worked out, more effective respiratory stimulants to be discovered. Our best institutions still suffer occasionally from epidemics of diarrhoea, although these have not been serious in recent years and have tended to spare babies in isolation incubators. There is still room for debate and further study upon the virtues of breast milk, high and low protein, whole or hydrolyzed protein, high and low fat, optimum mineral and vitamin intakes, vitamin vehicles, and a number of other items. But the progress to be made is small. We can maintain, protect, and feed the premature infant today with no great difficulty.

To illustrate this last point I may quote recent mortality statistics from three medical centers in New York City:

Weight Group at Birth	Percent Mortality				Total No. of Infants
	Center A	Center B	Center C	Average	
Under 1 000 g	86.2	87.0	94.4	88.6	211
1 000—1 499 g	36.2	44.8	42.6	41.4	331
1 500—1 999 g	19.7	20.5	15.6	19.0	654
2 000—2 500 g	11.8 [1]	5.6	4.6	5.7	1 464

[1] Includes infants up to 2 275 g only.

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These centers were similar in their case load; all of them received patients from outside the institution in substantial proportion. The nursing procedures differed only in minor details. The feeding policy differed widely. In Center A it consisted of a casein-enriched cow's milk with a generous quantity of an unsaturated vegetable fat substituted for butter. In Center B a formula of half skimmed cow's milk was used, whereas Center C employed a considerable amount of breast milk. Yet in spite of this wide discrepancy in feeding policy the mortality in each institution was virtually identical.

The crux of the premature problem which we are neglecting is shown at a glance by a study of current causes of death in premature infants.

Causes of Death in Premature Infants

New York City, 1945

No apparent cause	46.1 %
Anoxia	13.3 %
Infections, mostly pneumonia[1]	13.1 %
Haemorrhage	12.9 %
Malformations	9.7 %
Syphilis	0.6 %
Erythroblastosis	0.6 %
Miscellaneous	3.6 %

Similar data are reported from Chicago and elsewhere.[2] Roughly half of our premature deaths as a whole and an even larger proportion in the lowest weight group are dying from causes which are not apparent and which must be designated by the vague term immaturity. In the smallest weight group the proportion of these unexplained deaths exceeds 70 %.

It is this group of deaths from immaturity — deaths which occur particularly in the smallest infants and in the first days of life — that has remained virtually untouched by the advances

[1] Mostly aspiration pneumonia.

[2] Recent American statistics are reviewed by DUNHAM, E. C., Premature Infants, Children's Bureau Publication 325, U. S. Gov't Printing Office, Washington, 1948.

of recent years, and it is this group to which we should direct our attention. Credit is due to Finnish workers, particularly RAIHA and KLEMOLA, for demonstrating certain anatomical features of the immature infant which interfere with pulmonary expansion and oxygen exchange in the lungs and medulla, while other studies have revealed evidences of immaturity in the kidney, liver, and elsewhere. Significant as these contributions are, it may be questioned whether they play a large part in mortality. Most premature infants who die have breathed reasonably well for a day or two, nor is there evidence suggestive of a renal death. Physiological immaturity would seem to be the important factor, a subject about which information is almost wholly lacking.

The field is not entirely dark, however. There are indications that physiological immaturity involves the incomplete development of enzyme systems. LEVINE and GORDON (1) have shown that the aromatic amino acids phenylalanine and tyrosine are not metabolized in a normal manner. Carbonic anhydrase appears to be the only enzyme the development of which during foetal life has been followed in some detail. The studies of ASHBY (2) have shown that the development of this enzyme in various parts of the central nervous system occurs during the latter part of foetal life. With the many techniques now available for studying various enzymes in tissue homogenates, it is to be hoped that this lead will be followed, and that a knowledge of factors missing in the young premature infant will lead the way to their replacement. To label these infants »non viable» as is so often done is to accept defeat without a battle. We have an obligation to push back the limits of viability quite as clear as that to control disease in any form.

Summary

A consideration of recent statistics on premature mortality indicates that marked progress has been made, with the exception of the now predominant group of deaths due to »physiological immaturity». The need for studies of this obscure subject is stressed; a hopeful approach appears to be the study of tissue enzyme systems.

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Résumé

On s'aperçoit, en considérant les récentes statistiques de mortalité infantile, que des progrès remarquables ont été faits, à l'exception d'un groupe, actuellement prédominant, de morts par »immaturité physiologique». Il est donc nécessaire d'étudier ce sujet mal connu; sans doute pourra-t-on l'aborder par l'étude des systèmes d'enzymes tissulaires.

Zusammenfassung

Eine Betrachtung neuer Statistiken über die Mortalität von Frühgeburten zeigt, dass bemerkenswerte Fortschritte gemacht worden sind, ausgenommen die jetzt vorherrschende Gruppe von Todesfällen bei »physiologischer Unreife». Die Notwendigkeit der Erforschung dieses dunklen Gebietes wird betont. Ein versprechender Weg scheint zu sein die Gewebe-Forschung der Enzym-Systeme.

Sumario

Un estudio de las estadísticas recientes de mortalidad prematura indica que se han hecho notables progresos con la excepción del grupo de casos, ahora predominante, de muertes debidas a inmadurez fisiológica. Se recalca la necesidad de estudios sobre esta oscura materia; una manera prometedora de acercarse a este problema parece ser el estudio de los sistemas de las encimas del tejido.

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CHIEF: PROF. L. SALOMONSEN, M.D.

Familial Haemorrhagic Diatheses With Prolonged Bleeding Time (Pseudohaemophilia, Thrombopathias)

by

OLGA IMERSLUND

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Covering the period 1926—1933, v. WILLEBRAND has described certain familial cases of chronic haemorrhagic diathesis presenting the following characteristic features: bleeding time prolonged, number of thrombocytes usually normal, capillary resistance test positive in some cases, and coagulation time and clot retraction normal. At first he called this condition pseudohaemophilia but later on constitutional thrombopathia. Several similar cases, both with and without family histories, have subsequently been recorded under various names. In the American literature of recent years the term pseudohaemophilia occurs most frequently. Comprehensive surveys of the subject have been published by GEIGER and EVANS, MACFARLANE, QUICK, and, quite recently (1946), ESTREN, MEDAL, & DAMESHEK. The last-named could not find more than sixty two accurately described cases, and they have contributed eleven new cases to the total.

In 1947 I gave an account of six cases. Since then I have studied this condition in sixteen other cases which have led me to draw new conclusions.

My total material consists of twelve women and ten men whose ages at the first onset of symptoms ranged from a few days to about the beginning of school age. Their ages when they were first examined ranged from two months to seventy three years.

The clinical manifestations of these twenty two cases were identical with those of thrombopenia. Haemorrhages into the skin and mucous membranes and a tendency to bleed for a long

time following accidental and surgical wounds were observed. The appearance of the cutaneous haemorrhages tallied with that of thrombopenic purpura — petechiae and ecchymoses. I have never observed the quite large and flat haemorrhages which may occur in haemophilia, and an ordinary clinical examination showed nothing else of special interest — no enlargement of the lymphatic glands, liver, or spleen.

Table I gives a summary of the symptoms and of the findings in tests of the bleeding time, coagulation time, clot retraction, number of thrombocytes, and capillary resistance. This table shows that the last-named test was often positive, as in thrombopenic purpura. *The number of the thrombocytes* was usually normal, but in six cases it was *below normal* (a value below 200 000 per mm^3 was noted on a few occasions). My material includes two cases (11 and 18) which showed a rather low count on the only occasion upon which a thrombocyte count was made. They were brothers of patients who in other respects were typical representatives of this disease. The coagulation time was normal in all my cases. Clot retraction, investigated in altogether twelve cases, was normal in seven and slightly delayed in five. It was always investigated when the thrombocyte count was normal. The prothrombin time, serum proteins, fibrinogen, calcium, and ascorbic acid in the serum showed normal figures in the cases in which they were investigated. Apart from the effects of haemorrhages and infections, the examinations of the blood showed nothing else definitely pathological. There was nothing definitely pathological in the morphology of the thrombocytes in the cases in which they were investigated.

The manifestations of this disease were *markedly periodic* in these cases. At certain times the patients were very prone to develop blue patches in the skin and to suffer from nose-bleeding on slight provocation. At other times this tendency to bleed was but little marked. Menstrual bleeding and postpartum bleeding also showed this periodic feature. All the three women who had been confined stated that their tendency to bleed had increased during their pregnancies. The older patients stated that this tendency to bleed had been worse in childhood and adolescence, and

Table I

Case	Symptomatology	Date of Observation	Coag. Time (min.) (Capillary Tube)	Clot Retraction (24 hrs room temp.)	Bleeding Time (min.) (Duke)	Platelets × 1 000 (Fonio or Thomsen)	Tourniquet Test (Rumpel-Leede)
1. B. B. ♀ b. Aug. 9, 1938	Petechiae. Ecchymoses. Epistaxes. Bleeding after cuts.	1942	3		15	185 104 190	—
2. S. B. ♂ b. April 10, 1945	Petechiae. Ecchymoses. Epistaxes. Bleeding after cuts.	1945	2—5	Delayed	15— 3—4 hrs	42 287 249 548	−Once +Once
		1946	2		12—30	207	
3. K. I. ♀ b. Dec. 13, 1943	Petechiae. Ecchymoses. Epistaxes. Bleeding after cuts.	1946	3 2	Normal Normal	60 2 hrs	445 380	—
4. K. H. ♂ b. July 2, 1941	Petechiae. Ecchymoses. Epistaxes. Bleeding after cuts.	1945	3		15	8.3 10.6 16	−Once +Once
		1946	3		15 30 6 ½	300 282 153	
				Delayed	7	223	
5. S. O. ♀ b. June 2, 1903	Ecchymoses. Epistaxes. Bleeding after cuts and dental extractions. Melana. Duodenal ulcer 1937. Bleeding at operations.	1946	8		>40	488	+
5. L. Ø. ♂ b. Sept. 17, 1873	Ecchymoses. Bleeding after cuts and dental extraxtions.	1946	4 ½		20	254	+
7. E. U. ♀ b. June 6, 1941	Petechiae. Ecchymoses. Epistaxes. Bleeding from cuts.	1945	6 ½		60	423	−
8. T. B. U. ♂ b. May 5, 1879	Ecchymoses. Epistaxes. Bleeding after cuts and dental extractions.	1947	1 ½	Normal	57	375	÷
9. S. L. ♂ b. Feb. 19, 1935	Ecchymoses. Bleeding after cuts and dental extractions.	1947	3—6		>20	214	+
		1948	2—3		30	232	+
10. H. L. ♂ b. Mar. 16, 1942	Petechiae. Ecchymoses. Epistaxes. Bleeding after cuts.	1947	3—6		11	344	+
11. N. L. ♂ b. May 14, 1947	Petechiae. Ecchymoses. Epistaxes.	1947	8		8	163	+
12. K. M. ♀ b. Feb. 21, 1920	Ecchymoses. Epistaxes. Haematemeses. Gum bleeding. Menometrorrhagia.	1938			25	202	
		1939				308	
		1940	2 ½		>15	293	+
		1941			30	379	

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Table I (cont.)

Case	Symptomatology	Date of Observation	Coag. Time (min.) (Capillary Tube)	Clot Retraction (24 hrs room temp.)	Bleeding Time (Duke)	Platelets × 1 000 (Fonio or Thomsen)	Tourniquet Test (Rumpel-Leede)
13. A. G. R. ♀ b. Mar. 10, 1945	Ecchymoses. Bleeding after cuts.	1947	4	Normal	20	450	+
14. H. B. ♀ b. Aug. 14, 1914	Petechiae. Ecchymoses. Epistaxes. Bleeding after cuts and dental extractions. Menometrorrhagia. Postpartum bleeding. Bleeding after tonsillectomy.	1947	4	Delayed	15	524	+
15. A. R. ♀ b. Feb. 26, 1916	Petechiae. Ecchymoses. Bleeding after cuts. Gum bleeding. Menometrorrhagia. Postpartum bleeding. Bleeding after tonsillectoma.	1947 1948	3 4	Delayed Normal	>20	371	+
16. K. S. ♀ b. Nov. 9, 1915	Ecchymoses. Bleeding after cuts and dental extractions. Gum bleeding. Menometrorrhagia. Postpartum bleeding. Bleeding after tonsillectomy.	1944 1947	11 2	Normal	>40 22 >25	259 223 456	 +
17. G. J. ♂ b. Jan. 13, 1925	Ecchymoses. Epistaxes. Bleeding after cuts and dental extractions.	1947	4—5	Normal	45	382	+
18. N. J. ♂ b. Dec. 15, 1882	Ecchymoses. Epistaxes. Bleeding after cuts and dental extractions. Bleeding after tonsillectomy.	1948	5		30	138	+
19. H. J. ♂ b. Aug. 4, 1884	Ecchymoses. Petechiae. Bleeding after cuts and dental extractions. Gum bleeding. Bleeding at operations.	1947	4	Delayed	16	317	+
20. O. H. ♂ b. Feb. 2, 1933	Ecchymoses. Petechiae. Epistaxes. Bleeding after cuts and dental extractions. Bleeding after tonsillectomy.	1944 1946	3 6 1/2	 Normal	15—20 20	272 462	 +
21. H. G. ♀ b. Feb. 10, 1908	Ecchymoses. Epistaxes. Gum bleeding. Bleeding after cuts and dental extractions. Menometrorrhagias. Bleeding at operation. Haematuria after fracture of ribs.	1942	5		8 hrs	245 215	−
22. T. B. B. ♂ b. Aug. 3, 1942	Ecchymoses. Epistaxes.	1947 1948	3 1 1/2	Normal	15 15 16	120 481 238	 +

that it had shown itself when they had been operated on. Some patients had suffered from severe bleeding after certain operations, but not after all. Thus Case 21 (H.G.) suffered from prolonged bleeding after a splenectomy in 1933, but there was no extensive haemorrhage when her appendix was removed in 1938. Case 20 (O.H.) suffered from prolonged bleeding after a dental extraction at the age of nine, but when teeth were extracted two years later he did not bleed excessively. Case 16 (K.S.) bled profusely after a tonsillectomy at the age of seven, but only slightly after an appendectomy at the age of twenty eight.

The bleeding time also varied much from time to time in the same patient, and occasionally it was almost normal. The capillary resistance test was found positive on some occasions, negative on others. Case 15 (A.R.) showed on one occasion a slight delay in clot retraction, but a year later this was found to be normal.

There was no relationship between the number of the thrombocytes and the tendency to bleed. The bleeding time was found to be prolonged even when the number of the thrombocytes was normal. When it was below normal, there was no increase in the tendency to bleed. Special attention was paid to Case 4 (K.H.) during a period when the number of the thrombocytes was much reduced (8 300—16 000 per mm^3) and at other periods when it was normal. The onset of severe thrombopenia did not entail an appreciable increase in the tendency to bleed.

In nineteen of the twenty two cases the disease was shown to be familial (see Table II and the pedigrees, Figs. 1—8). The pedigrees were in part compiled on the basis of personal communications from members of these families still alive, in part on the basis of parish records and national census lists. The twenty two patients originate from fifteen sibships with affected individuals. Table II gives the total number of children and those who suffered from this disease in the fifteen sibships. In these fifteen sibships there were altogether twenty six cases of the haemorrhagic diathesis. Three members of these sibships reported to have suffered from the same diathesis died before my investigation started. Case 14 has a sister with the same disease,

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Table II

Sibships of children suffering from haemorrhagic diatheses with prolongation of bleeding time.

Sibship No.	No. of Children	Haemorrhagic Diathesis			Fatal Haemorrhage	
			♀	♂	♀	♂
I	8	3	1	2	1	1
II	4	2	2		1	
III	2	1		1		
IV	3	1	1			
V	9	1		1		
VI	4	1	1			
VII	5	1		1		
VIII	5	4	2	2	1	
IX	5	1	1			
X	1	1	1			
XI	6	4	3	1		
XII	4	2		2		
XIII	2	1		1		
XIV	11	2	2			
XV	1	1	1			
Total	70	26	15	11	3	1

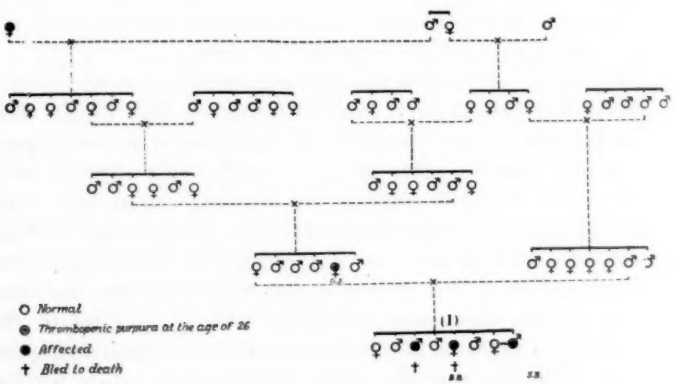

Fig. 1. Pedigree of the sibship I.

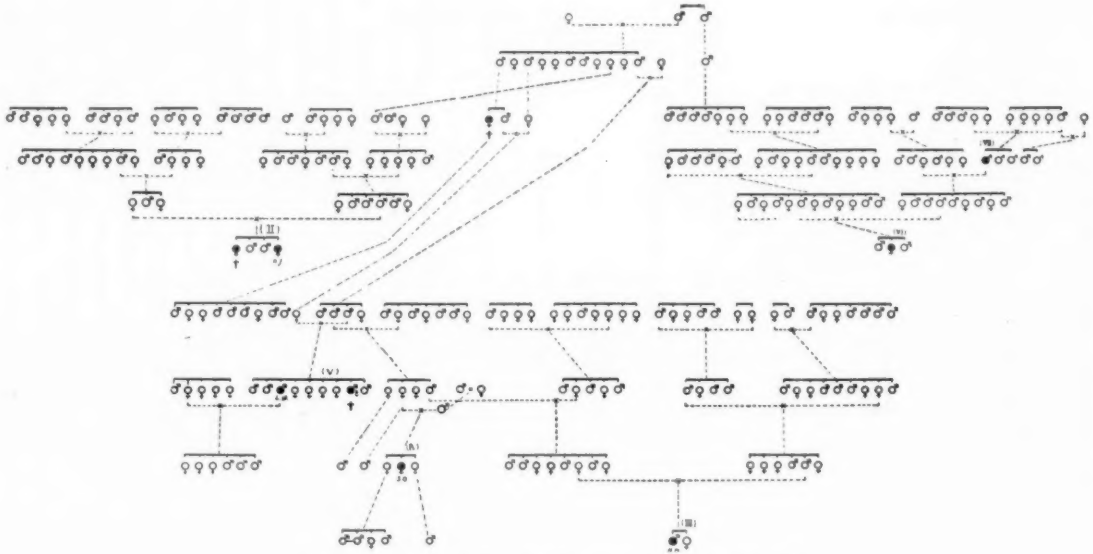

Fig. 2. Pedigree of the sibships II, III, IV, V, VI, VII.

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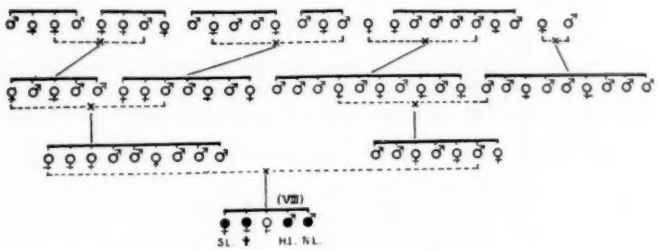

Fig. 3. Pedigree of the sibship VIII.

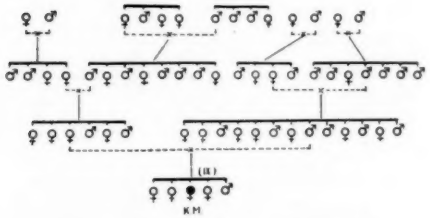

Fig. 4. Pedigree of the sibship IX.

to judge by the available information about her. Fig. 2 shows that the sibships II—VI are related to one another and the sibships VI and VII are related to one another. Fig. 5 shows that the sibships X, XI, and XII represent three generations.

This familial occurrence of the disease suggests that it is *hereditary*. The clinical features of these cases are so much alike that they may well indicate one and the same disease. But the results of an investigation of the hereditary conditions suggest that we are dealing with at least *two different hereditary types* of haemorrhagic diathesis, one with a *recessive* factor inherited, the other with a *dominant* factor.

The pedigree of the sibship I points definitely to a recessive factor. Here there occurred three cases of haemorrhagic diathesis in children whose parents were related to one another but were healthy. These parents were examined.

The other pedigrees, with the exception of those of the sibships X, XI, and XII, may also be indicative of a recessive

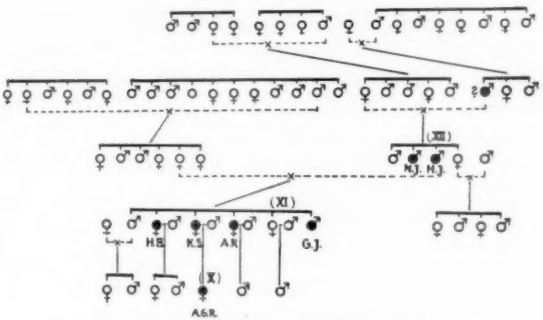

Fig. 5. Pedigree of the sibships X, XI, XII.

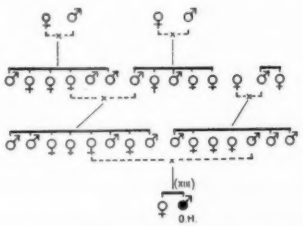

Fig. 6. Pedigree of the sibship XIII.

factor. No definite case of a haemorrhagic diathesis could be found on examination of the parents of the sibships II, III, VIII, XII, and XV. The parents of the other sibships are said to have been healthy. The parents of the sibship V were also related to one another. It is, however, difficult in all the above-named pedigrees to exclude a dominant form of inheritance, as little is known about possible subclinical manifestation of the disease. In the sibship VIII there are rather many affected children for a recessive form of inheritance.

The pedigrees of the sibships X, XI, and XII are definitely indicative of a dominant factor. In these families the disease can be traced through three generations, and there were no consanguine marriages. The disease was passed on from Case 19 (H.J.) to three daughters, Cases 14 (H.B.), 15 (A.R.), and 16 (K.S.) and to a son, Case 17 (G.J.). From the daughter Case 15

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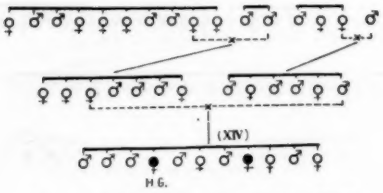

Fig. 7. Pedigree of the sibship XIV.

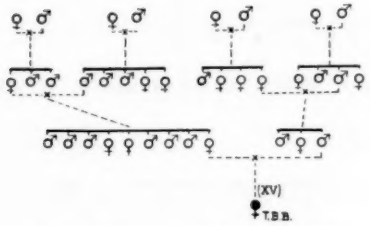

Fig. 8. Pedigree of the sibship XV.

(A.R.) the disease was transmitted to her daughter, Case 13 (A.G.R.), the transmission being apparently by a single dominant factor. Those who showed no signs of the disease had healthy children, whereas those who showed such signs had both ailing and healthy children.

The results of the investigations carried out on these patients failed to show that the thrombocytes played any part of importance in the tendency to bleed. If defective functioning of the thrombocytes were the main cause of the tendency to bleed, one would expect an exacerbation of the symptoms when the thrombocyte count was very low. This was not, however, the case, and the thrombocytes and the tendency to bleed behaved quite independently of one another. In other words, I found nothing to show that a tendency to bleed was due to so-called thrombopathia. It is also unlikely that defective functioning of the thrombocytes could determine the marked periodicity of the symptoms.

I have been unable to discover any hard and fast line between the cases in my material and the *chronic forms of essential thrombopenia*. The thrombopenia observed in some of my patients

may well be termed idiopathic for want of the demonstration of any evident cause thereof. With regard to the relationship of the thrombocytes to the tendency to bleed, it may be noted that in essential thrombopenia and secondary forms of thrombopenic purpura there is also no absolute relationship demonstrable between the thrombocyte count and the tendency to bleed (see the papers of MACKAY and MACFARLANE). In certain phases of essential thrombopenia, the bleeding time may be prolonged even though the number of thrombocytes is normal. On the other hand, the bleeding time may be normal in spite of a very low thrombocyte value. *Thrombopenia seems to be a coincident phenomenon of no pathogenetic significance.*

In view of the similarity of my patients to patients suffering from essential thrombopenia, I am inclined to believe that the underlying cause of the haemorrhages is one and the same. This pathogenetic factor, which I suspect is common to both, does not seem to be concerned with the thrombocytes. A relationship between thrombopenic and non-thrombopenic purpura also seems to be indicated by the fact that a relation of one of the families in my material suffered from acute thrombopenic purpura. A sister of the mother of sibship I suffered at the age of twenty six from a transitory haemorrhagic diathesis with thrombopenia when she contracted acute hepatitis. Her haemorrhagic diathesis may have been a manifestation of the same haemorrhagic diathesis observed in sibship I, and it may have been an expression of the same hereditary predisposition brought out by the acute hepatitis. As the pedigree of sibship I shows, the parents of this patient were also related to one another.

Summary

The author has studied clinical manifestations and hereditary conditions in twenty two cases suffering from chronic haemorrhagic diathesis with the same features as those described by v. WILLEBRAND: prolonged bleeding time, usually normal number of thrombocytes, normal coagulation time.

The author has found nothing to show that the tendency to bleed is due to so-called thrombopathia.

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The results of the investigation of hereditary conditions suggest the existence of at least two different hereditary types, one with a recessive factor and the other with a dominant factor inherited.

Résumé

L'auteur a étudié les manifestations cliniques et les antécédents héréditaires chez 22 malades souffrant d'une diathèse hémorragipare du même type que celle des cas décrits par WILLEBRAND. Temps de saignement prolongé, nombre des thrombocytes pratiquement normal, temps de coagulation normal. L'auteur n'a rien trouvé qui prouverait que la tendance hémorragipare fût en rapport avec une soi-disant thrombopathie. Les résultats des investigations cliniques et de la recherche des facteurs héréditaires suggèrent l'existence d'au moins deux types héréditaires différents: l'un avec un facteur d'hérédité récessive, l'autre avec un facteur dominant.

Zusammenfassung

Die Verfasserin untersuchte die klinischen Symptome und hereditären Bedingungen bei 22 Fällen von chronischer hämorrhagischer Diathese mit denselben Merkmalen, wie solche von WILLEBRAND beschrieben wurden. Blutungszeit verlängert, Zahl der Thrombozythen gewöhnlich normal, Gerinnungszeit normal.

Die Verfasserin hat nichts gefunden, was darauf hinweist, dass die Tendenz zu Blutungen auf sogenannter Thrombopathie beruhe.

Die Untersuchungsresultate der hereditären Bedingungen deuten auf das Vorhandensein von mindestens zwei verschiedenen hereditären Typen, der eine mit einem rezessiven Faktor erblicher Art, der andere mit einem dominanten Faktor.

Sumario

El autor ha estudiado las manifestaciones clínicas y las condiciones hereditarias de 22 casos de diátesis hemorrágica crónica, con los mismos caracteres descritos por WILLEBRAND. Pro-

longación del tiempo de sangria, número de trombocitos en general normal, e igualmente el tiempo de coagulación.

El autor no ha podido encontrar nada que demuestre que esta tendencia a sangrar se deba a una llamada trombopatía.

Los resultados referentes a las condiciones hereditarias sugieren la existencia de por lo menos dos tipos hereditarios distintos, uno con herencia de un factor recesivo y otro con un factor dominante.

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FROM THE PAEDIATRIC CLINIC OF KAROLINSKA INSTITUTET AT THE NORRTULL HOSPITAL, STOCKHOLM.
CHIEF: PROF. A. WALLGREN.

The Disappearance of Rheumatic Carditis and the Delayed Appearance of Rheumatic Heart Disease

by

ERIK JACOBSSON

The reduction in the incidence of juvenile rheumatic fever that has been evident in Sweden during the past few years ought after a time to result in a decrease in the number of cases of rheumatic heart disease. Whether this reduction is a permanent one or not, time alone will tell, but judging by the tendency displayed by the disease in the past to occur in intercurrent waves, we have some justification for expecting that there will be a fresh increase in the incidence within the not too distant future. Whatever the situation may be in this respect, the disease has not yet been entirely eradicated, and the cardiac affections due to rheumatic fever still constitute a not inconsiderable proportion of the organic heart disorders. Rheumatic fever, as we all know, is in the nature of a generalized mesenchymal disease with a special affinity for the heart. This fact, as well as the lack of a specific therapy, deprives us of the possibility of effectively preventing the development of permanent cardiac disorder in these patients.

While we cannot prevent the development of rheumatic cardiac disorder, we can, on the other hand, do quite a lot in the way of preventing a permanent heart lesion from being subjected to overstrain as the result of the individual's mode of life (an unsuitable occupation, excessive sport, and so on). According to all experience hitherto gained, overstrain of this type has, in the long run, an injurious effect on the heart and its functions. It is therefore also of great importance to know to what extent an attack of rheumatic fever gives rise to permanent heart damage

and also whether a cardiac affection can be expected to manifest itself subsequently during the, rheumatically speaking, symptom-free stage.

The occurrence of cardiac damage in persons who have passed through an attack of rheumatic fever without displaying sure signs of heart involvement during the course of the attack and in spite of the absence of subsequent, definitely established recurrences has not been accorded much attention in the rheumatic literature. A few publications on this aspect are available, however. DUCKETT JONES, for instance, had three hundred and twenty eight children in a group of one thousand with rheumatic fever who showed no unequivocal signs of cardiac involvement at the time of their discharge from the hospital. Of these, seventy one subsequently developed cardiac lesions of greater or lesser severity, but in roughly half of these the heart damage arose in connection with a recurrent attack. BLAND and JONES had three hundred and fourteen patients who were left without demonstrable damage to the heart after recovering from their initial rheumatic infection. Twenty-four of these patients who had no recurrence throughout a ten year observation period subsequently developed characteristic signs of cardiac involvement. Among her six hundred and seventy three children, WILSON had four hundred and twenty seven cases in whom, in consideration of the cardiac involvement detected at a later stage, a subclinical carditis must presumably have been present. The heart damage in these cases was, however, milder than in other cases. But no difference with respect to the severity of the cardiac lesions was demonstrated between patients who had originally had choreatic symptoms and patients who had had growing or joint pains or polyarthritis.

It is a well known fact that the signs and symptoms of a carditis (endocarditis, myocarditis, and pericarditis) vary greatly during an attack of rheumatic fever, and it has been assumed in a general way that the more severe the carditis symptoms are the more serious the future outlook for the heart will be, and vice versa, while very slight or no signs of carditis imply a more hopeful prognosis. Provided that the individual in question does not have a recurrence of his rheumatic fever, it ought to be

possible, with this as a basis, to draw certain conclusions regarding the outlook for the heart for the future. This is also possible, as I shall show further on, but it is possible only to a certain extent. On the other hand, a definite recurrence of the disease naturally reduces the prospects for the heart to a greater or lesser extent.

In order to gain an idea of the persistence of heart lesions due to rheumatic fever it is therefore necessary to confine oneself for the most part to a study of those cases where there has been no definitely established subsequent recurrence. The same thing applies to the question of whether a rheumatic cardiac affection can arise in an individual who has passed through an attack of rheumatic fever without displaying any proven signs of carditis, or with only mild carditis symptoms during the attack, and who has had no definitely established recurrence. In my series of cases from Gothenburg (JACOBSSON 1946) there were three hundred and seven patients who had had no recurrence of the disease over an observation period of four to twenty years. In Table 1 I have assembled these cases in order to show the occurrence of cardiac damage in this material after an observation time of at least four and up to twenty years. The cases have also been classified on the basis of the presence of carditis in connection with their illness and the severity of the cardiac involvement. The cardiac affection was considered to be *not definitely established* in cases where no definite signs of active carditis could be detected during the active infection either at the physical examination or by an electrocardiographic or roentgenographic examination. In cases with carditis, this was interpreted (using approximately the same method of classification as that used by WILSON 1940) as *mild* when the signs of cardiac affection were of slight intensity (tachycardia, valvulitis, mild myocarditis with retardation of the P—Q time, or other electrocardiographic changes of an inconsiderable and transient nature) and of less than one month's duration.

As will be seen from the table, rheumatic carditis may disappear completely without leaving any traces whatsoever of permanent heart damage, despite the fact that the original cardiac affection was of a fairly severe nature. On the other hand, sure

Table 1

Cardiac affection at follow-up in relation to severity of initial carditis in all patients wholly without recurrence.

Relation between severity of initial carditis and that of final cardiac affection tested for heterogeneity by the χ^2-method.

Nature of Initial Carditis	No. of Cases With No Recurrences	Nature of Cardiac Affection at Follow-Up					
		No Heart Disease + Possible Heart Dis.	Functional Classification[1]			All Cases With Roentgenographic Heart Changes	Electrocardiographic Heart Changes
			Class I	Class II	Classes III and IV		
Not Definitely Established ...	59	33 55.9 % ± 6.5	25 42.4 % ± 6.4	1 1.7 % ± 1.7	—	9 15.3 % ± 4.7	6 10.2 % ± 3.9
Mild	189	72 38.1 % ± 3.5	100 52.9 % ± 3.6	17 9.0 % ± 2.1	—	51 27.0 % ± 3.2	31 16.4 % ± 2.7
Moderate or Severe	59	16 27.1 % ± 5.8	31 52.5 % ± 6.5	12 20.3 % ± 5.2	—	23 39.0 % ± 6.4	13 22.0 % ± 5.4
Total	307	$\chi^2 = 10.6$, $P < 0.01$, d. f. 2		$\chi^2 = 12.0$, $P < 0.01$, d. f. 2		$\chi^2 = 8.4$, $0.01 < P < 0.02$, d. f. 2	$\chi^2 = 3.1$, $P > 0.20$, d. f. 2

[1] According to the Criteria Committee of the New York Heart Association: »Nomenclature and Criteria for Diagnosis of the Heart».

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signs of carditis need not necessarily have been present during the initial attack to serve as the foundation for the subsequent development of an unequivocal cardiac lesion. But as might be expected, the risk of subsequent permanent cardiac disorder increases in proportion to the severity of the initial carditis. And this feature is particularly noticeable with regard to the risk of serious cardiac disorder (belonging to classes II—IV, from the functional standpoint). Thus the milder the signs of carditis, the greater the chances that an individual with rheumatic fever will not develop permanent heart damage. The chances are greatest in those cases where no sure signs of carditis were demonstrated during the acute stage. (From the statistical point of view, the conditions described here are very probable, as will also be seen from the values of the χ^2 analysis shown in the table.)

We usually count on there being a certain amount of cardiac involvement in every case of acute rheumatic fever during the acute phase, although it is not always detectable with our methods of examination, or may not be discovered because the examinations are not made often enough, or because the signs and symptoms are not infrequently very transient and therefore disappear rapidly. These transient heart lesions, as well as those not detectable with our present diagnostic aids, may, of course, give rise subsequently to scar formations which become exaggerated as time goes on and thus produce constriction and retractions resulting finally in clinically demonstrable heart damage. On the other hand, it is, naturally, conceivable that these individuals who showed no signs of carditis during the acute infection may subsequently pass through one or more subclinical attacks of rheumatic fever and that during these the heart may be involved to such an extent as finally to produce a definite cardiac lesion in some form.

A more remarkable finding, perhaps, is that a definitely established valvular lesion following an acute infection may subsequently disappear entirely without leaving any traces whatsoever. I have a number of such cases in my material. One of these patients was treated at the age of ten for two months at the Children's Hospital in Gothenburg and when discharged was noted

as suffering from a definite valvular deformity in the form of insufficiency and stenosis of the mitral valve. At an examination twenty years later no signs of heart disease could be detected. He had no subjective symptoms from the heart, the heart tones were pure, the electrocardiogram was absolutely normal, and roentgen examination revealed a normal heart with a volume of 290 cc per square meter of body surface. — Another boy had his initial attack at seven years of age and was treated for two and a half months at the hospital during the attack. When discharged he had a combined aortic and mitral valve defect of such severity that Professor Wallgren expressly considered it would be permanent. When examined twenty years later he was found to be completely healthy in all respects, he was a keen sportsman, and among other feats he had recently bicycled from Gothenburg to Stockholm (a distance of about 500 kilometers) in three days. The heart tones were pure even after strenuous exercise, the electrocardiogram was completely normal, and roentgen examination of the heart showed a normal heart shadow and a volume of 480 cc per square meter of body surface. — Another patient not only had established endopericarditis when in the hospital in 1923 at the age of thirteen but also signs of cardiac insufficiency with a fairly pronounced tachycardia, and in addition to this his general condition was affected. Many years later, when he was to start his compulsory military training, he applied to the Children's Hospital for a certificate regarding his heart, but all that could be detected was a presystolic premature beat in the first tone at the apex; otherwise, the tones were pure. When I examined him twenty years after the initial attack his heart tones were absolutely pure even after exertion, the electrocardiogram was normal, a roentgenogram of the heart showed a normal shadow with a volume of 420 cc per square meter of body surface, and he complained of no symptoms whatsoever.

In this connection it is of interest to mention that even persons who had passed through several recurrent attacks with more or less pronounced signs of carditis on different occasions displayed no traces whatsoever of cardiac disorder when I examined them after periods of up to twenty years after the initial attack.

Table 2

Nature of cardiac affection in relation to number of recurrent attacks

Groups With the Following Number of Recurrences	Survivors Examined at Follow-Up	Nature of Cardiac Affection				
		No Heart Disease	Possible Heart Disease	Functional Classification:		
				Class I	Class II	Class III
0	307	76	45	156	30	—
		121				
		39.4 % ± 2.8		50.8 % ± 2.9	9.8 % ± 7.1	
1	151	35	12	74	29	1
		47				
		31.1 % ± 3.8		49.0 % ± 4.1	19.2 % ± 3.1	0.7 % ± 0
≧ 2	74	7	4	39	21	3
		11				
		14.9 % ± 4.1		52.7 % ± 7.0	28.4 % ± 5.2	4.1 % ± 2
		$\chi^2 = 16.7$, $P < 0.001$, d. f. 2			$\chi^2 = 25.6$, $P < 0.001$ d. f. 2	

Out of one hundred and fifty one cases with only one recurrence (see Table 2), forty seven (31.1 %) showed no sure signs of cardiac affection, and among seventy four cases with three or more attacks of rheumatic fever there were no less than eleven (14.9 %) without sure signs of heart damage, despite the fact that the majority of them had had signs of carditis at some time during their rheumatic attacks. It will also be seen from the table that the risk of permanent damage to the heart rises as the number of recurrences increases, this risk being statistically significant.

There were also a number of cases of chorea minor in my series of rheumatic fever cases. This is a disease which, in the opinion of earlier authors and even of a few investigators today, ought not to be regarded as a form of rheumatic fever, partly because of the fact that it is associated with carditis symptoms to a far lesser extent than the arthritic form of rheumatic fever. It is of interest to point out that the chorea minor cases in my ma-

Table 3

Nature of cardiac affection at follow-up classified according to nature of initial manifestation in relation to occurrence or non-occurrence of recurrent attacks.

Initial Manifestation	Survivors Examined at Follow-Up	Nature of Heart Affection					Roentgenographic Heart Changes	Electrocardiographic Changes
		No Heart Disease	Possible Heart Disease	Functional Classification				
				Class I	Class II	Class III		
Arthritic Symptoms With or Without Carditis + Carditis Alone:								
Without Recurrences	256	61(23.8 %)	40(15.6 %)	129	26	—	69	41
		101		50.4 % ± 3.1	10.2 % ± 1.9		27.0 % ± 2.8	16.0 % ± 2.3
		39.5 % ± 3.0						
With Recurrences	176	34(19.3 %)	15(8.5 %)	87	37	3	74	47
		49		49.4 % ± 3.8	21.0 % ± 3.1	1.7 % ± 1.0	42.0 % ± 3.7	26.7 % ± 3.3
		27.9 % ± 3.4						
Chorea:								
Without Recurrences	51	15(29.4 %)	5(9.8 %)	27	4	—	14	9
		20		52.9 % ± 7.0	7.8 % ± 3.8		27.4 % ± 6.2	17.6 % ± 5.3
		39.2 % ± 6.8						
With Recurrences								
a) All cases with recurrences.	49	8(16.3 %)	1(2.0 %)	26	13	1	21	12
		9		53.1 % ± 7.0	26.5 % ± 6.3	2.0 % ± 2.0	42.8 % ± 7.1	24.5 % ± 6.1
		18.4 % ± 5.5						
b) Cases in which there were always choreatic manifestations in the recurrent attacks.	32	6(18.8 %)	1(3.1 %)	19	6	—	11	8
		7		59.4 % ± 8.7	18.7 % ± 6.9		34.4 % ± 8.4	25.0 % ± 7.6
		21.9 % ± 7.3						

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terial showed exactly the same features as other cases of rheumatic fever with respect to the risk of recurrences, the risk of permanent heart damage, and so on. In those cases where chorea was present at the initial attack but where there were subsequent attacks with arthritis and carditis, or carditis alone, it is perhaps not so surprising that valvular lesions developed as a sequel of these attacks. But it is more remarkable to find that the risk of the occurrence of permanent cardiac damage is the same as for other cases of rheumatic fever in those cases where not only the initial attack but all subsequent recurrences were marked by the presence of chorea (see Table 3). This is the more remarkable seeing that in these cases with choreatic manifestations, carditis was present in conjunction with the choreatic attacks to a far lesser extent than in the other cases of rheumatic fever. This fact seems to me to indicate that, at some time subsequent to the initial attack, these individuals pass through slight but nevertheless subclinical rheumatic attacks with a certain amount of cardiac involvement.

The evidence from this material thus shows

t h a t in connection with rheumatic fever the risk that permanent damage to the heart will arise increases in proportion to the severity of the initial carditis, but

t h a t the initial cardiac lesions may disappear so completely that no signs of them can be discovered at a later stage, even in cases where sure signs of cardiac damage were established immediately after the clinical recovery from the rheumatic attack.

The findings also indicate t h a t even if the heart was wholly, or almost wholly, spared from involvement during the attack of rheumatic fever, a valvular lesion could subsequently develop without the occurrence of any clinically demonstrable recurrent attacks; the risk of this was lowest, however, among those cases where no signs whatsoever of carditis had been demonstrated.

Summary

In a follow-up examination of patients who had rheumatic fever during childhood the author studied in particular the disappearance of the rheumatic carditis as well as the likelihood of

the delayed appearance of heart damage. He has found that the risk that permanent cardiac disorder will develop in connection with rheumatic fever increases in proportion to the severity of the initial carditis. But the initial carditis may clear up so completely that no permanent cardiac affection can be detected at later examinations. Even though during an attack of rheumatic fever the heart may be completely, or almost completely, spared from carditis, a valvular lesion may nevertheless develop at a later stage.

Résumé

Dans l'examen suivi de patients qui avaient eu une fièvre rhumatismale dans leur enfance, l'auteur étudia en particulier la disparition de la cardite rhumatismale, de même que la probabilité d'un apparition retardée de lésions cardiaques. Il a trouvé que le risque qu'un trouble cardiaque permanent puisse se développer, en connexion avec une fièvre rhumatismale, augmente en proportion de la gravité de la cardite initiale. Mais la cardite initiale peut disparaître à tel point qu'aucune affection cardiaque permanente ne pourra être décelée lors d'examens ultérieurs. Alors même que le cœur, lors d'une attaque de fièvre rhumatismale, peut être complètement, ou presque complètement, épargné par la cardite, une lésion valvulaire peut néanmoins se développer par la suite.

Zusammenfassung

Bei einer Reihe von Patienten, die in ihrer Kindheit an rheumatischem Fieber erkrankt waren, hat der Verfasser das Fehlen einer rheumatischen Karditis und die wahrscheinliche Verzögerung eines Herzschadens genauestens überprüft. Er fand, dass das Risiko dauernder Herzschädigung in Verbindung mit rheumatischem Fieber im Verhältnis zur Schwere der Initialkarditis wächst. Die Initialkarditis kann jedoch so völlig verschwinden, dass bei späteren Untersuchungen keine dauernde Herzaffektion entdeckt werden kann. Wenn auch das Herz beim rheumatischen Fieber völlig oder nahezu völlig von einer Karditis verschont bleiben mag, so kann sich ein Klappenschaden später dennoch entwickeln.

Sumario

En examenes seguidos de pacientes que habían tenido una fiebre reumatismal en su infancia, el autor estudía en particular la desaparición de la carditis reumatismal, y la posibilidad de la aparición tardia de lesiones cardíacas. El encuentra, que el riezgo de que pueda desarrollarse una lesión cardíaca permanente en conección con una fiebre reumatismal, aumenta proporcionalmente con la gravedad de la carditis inicial. Pero la carditis reumatismal puede desaparecer a tal punto, que no puede demostrarse en los examenes ulteriores ninguna afección cardíaca permanente. Pero aunque el corazon, luego de un ataque reumatismal puede encontrarse completamente o casi completamente respetado por la carditis, puede desarrollarse de todas maneras una lesión valvular.

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FROM THE CENTRAL LABORATORY OF KRONPRINSESSAN LOVISA'S CHILDREN'S HOSPITAL AND THE CENTRAL LABORATORY OF ST. ERIK'S HOSPITAL, STOCKHOLM.

A Micromethod for the Colorimetric Determination of Total Serum Proteins and of Serum Albumin and Globulin

by

BERTIL JOSEPHSON and HANS ANDURÉN

An abundance of micromethods for the determination of serum proteins has been published. In our experience, however, none of these methods satisfies the demand for reliability combined with simplicity.

In 1948 KIBRICK and BLONSTEIN found that comparatively good conformity between salt fractionation and cataphoretic analyses was reached if the globulins were salted out in 26 per cent Na_2SO_4-solution. Their results have been reinvestigated in one of these laboratories (by Dr. K. BONNICHSEN, not published). Using OLHAGEN's (1945) cataphoretic method BONNICHSEN found slightly lower albumin and higher globulin values than with the salting out in 26 per cent Na_2SO_4.

Recently GORNALL, BARDAWILL, and DAVID (1949) published a thorough examination of all the steps and reagents in the KINGSLEY (1942, 1944) method of determining the proteins by means of the biuret reaction. Their investigations resulted in a modification of this method in which the reagents were made up in an appropriate way. However, they did not investigate the salting out reagent but stuck to the 22.6 per cent sodium sulfate.

We have changed this reagent to a 27 per cent sodium sulfate solution according to KIBRICK and BLONSTEIN and read the colour on a Pulfrich step photometer, but otherwise we have used the modification of GORNALL, BARDAWILL, and DAVID. In this way we have obtained results in comparatively good agreement both with

cataphoretic analysis and with Kjeldahl determinations. The best transmission curve with the step photometer was obtained when a 10 mm cuvette was used and the colour read through filtrum S 53 against a blank of biuret reagent and sodium sulfate solution. Of course a photoelectric colorimeter can be used, but in this case reading on the step photometer is to be preferred to the use of a photoelectric colorimeter of ordinary type.

To meet the increasing need for protein determinations in small quantities of plasma, especially in samples from small children, we have worked out a micromodification of this method which has been in use in these laboratories for several months.

The reagents were the same as those described in the article by GORNALL, BARDAWILL, and DAVID (1949) with the exception that their 22.6 per cent sodium sulfate solution was changed to a 27 per cent solution. This solution, which is over-saturated at room temperature, must be stored at about 37°.

A calibration curve was made up according to GORNALL, BARDAWILL, and DAVID. The solution, containing only biuret-reagent and Na_2SO_4 but no protein, was used as blank in the step photometer. As the curve is a straight line passing origo a multiplication factor can be used instead of the curve. This factor is so chosen that when it is multiplied by the extinction coefficient the protein concentration is obtained. We found the factor to be 30. The curve must be controlled when new biuret-reagent is used.

Method

A. *Total Protein.* Pipette into a test tube 0.05 ml serum, add 0.95 ml 27 % Na_2SO_4, and mix without shaking. Add 4 ml biuret-reagent and mix. Read with filter S 53 not less than 30 or more than 90 minutes later in a 10 mm cuvette against a blank made up of 1 ml Na_2SO_4 and 4 ml biuret-reagent. The concentration will be found from the calibration curve.

B. *Albumin-Globulin.* Pipette 0.1 ml serum into a small test tube (about 10×50 mm), stopper, and leave at about 37° for c. 15 min. At the same time warm a small funnel, a good filter paper (Munktell 00), and a 1 ml and a graduated 2 ml

pipette to 37° together with the tube. Using a pre-warmed pipette, add 1.9 ml Na_2SO_4 solution to the tube with serum. Mix without shaking. Let stand at 37° for one hour or more. Filter at 37° through a pre-warmed paper with the pre-warmed funnel covered by a watch glass. The filtrate must be clear. If it is not, filter again through the same paper. It is easier to obtain 1 ml clear filtrate in this way than by centrifuging with ether. With a pre-warmed pipette transfer 1.0 ml of the filtrate into a test tube. Add 4 ml biuret-reagent. The subsequent procedure is identical with that for total protein after the addition of the biuret-reagent. The albumin concentration is read from the same calibration curve as the total protein. The globulin concentration is found by subtracting the albumin from the total protein concentration.

KIBRICK (1949) found the intensity of the biuret colour to be subject to temperature variations greater than those found by GORNALL, BARDAWILL, and DAVID (1949). Using the modification described above we have found these variations to correspond to 0.04—0.06 per cent protein per 1° C between 6° C and 35° C. This means that the ordinary variations in room temperature are of little influence but that greater variations should be avoided. An approximative temperature correction can be attained by addition or subtraction of 0.05 to or from the percentage figure for each degree below or above the temperature at which the standard curve was made up. If the working temperature is higher the correction should be subtracted from the apparent result and vice versa.

Results

Table 1 shows the first results we obtained with this method and the corresponding results with the macromethod and with Kjeldahl determinations.

In small children and other patients in whom a vein puncture cannot be carried out, 0.1 ml serum can be obtained conveniently from a small quantity of blood if the centrifuge and tubes described by JOSEPHSON (1943) are used.

Table 1

Results of the microtechnique compared with the modified macrotechnique of GORNALL, BARDAWILL, and DAVID and with KJELDAHL determinations.

Sample No.	Microtechnique		Macrotechnique		KJELDAHL	
	Total	Albumin	Total	Albumin	Total	Albumin
1	5.9		6.0	2.2	6.1	2.3
2	6.2		6.4	3.6	6.4	4.3
3	8.1		8.0	3.6	8.0	3.6
4	8.0		9.1	2.4	9.9	2.7
5	6.6		6.3	4.0	7.0	4.4
6	7.0		7.9	2.9	7.9	3.0
7	5.5		5.5	3.5	5.8	3.6
8	7.2		7.0	3.5	5.8	4.2
9	5.7		5.8	3.2	5.9	3.4
10	6.8		6.8	4.1	6.9	4.4
11	5.6		5.5	2.9	5.6	3.1
12	7.1		7.3	3.5	7.0	3.4
13	5.8	2.0	6.0	2.1	5.9	2.2
14	5.6	3.1	5.8	3.0	5.8	3.1
15	7.2	4.4	7.3	4.5	7.0	4.5
16	7.7	4.5	7.8	4.8	7.6	4.4
17	7.2	2.3	7.2	2.0	7.1	2.2
18	8.5	3.5	8.4	3.5	8.4	3.5
19	7.2	4.7	7.2	4.4	7.3	4.3
20	9.2	5.7	9.2	5.4	9.2	5.4

Summary

A micromethod for the colorimetric determination of serum proteins is described. The total protein concentration can be determined in 0.05 ml serum and the albumin in 0.1 ml.

Résumé

Une microméthode est décrite pour la détermination colorimétrique des protéines de sérum. La concentration totale de protéine peut être déterminée en 0.05 ml de sérum et l'albumine en 0.1 ml.

Zuzammenfassung

Eine Mikromethode für die kolorimetrische Bestimmung von Serumproteinen wird beschrieben. Totalprotein kann in 0.05 ml Serum bestimmt werden und Albumin in 0.1 ml.

Sumario

Se describe un micro-método para la determinación colorimétrica de seroproteínas. Se puede determinar en 0.05 ml la proteína total y en 0.1 ml la albúmina.

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FROM THE PAEDIATRIC DEPARTMENT OF THE GENERAL HOSPITAL, UMEÅ.
CHIEF: KURT KAIJSER, M.D.

Some Views on the Frequency of Premature Children in a Northerly Part of Sweden

by

KURT KAIJSER and FREDRIK FRÄNKEL

»It would be desirable that suitable treatment, and more especially hospital treatment, should be available for as many as possible of the more markedly premature infants.

It is desirable that, to as great an extent as possible, these infants should be sent direct to a paediatric institution from the maternity hospital.»

A. LICHTENSTEIN, 1916.

»A paediatric objective to be aimed at would be to install a paediatric department in every county hospital and to start, as soon as possible, with some of the General Hospitals in the Northern Counties.»

A. LICHTENSTEIN, 1922.

Thus did Professor Lichtenstein, at an already early stage of the more modern paediatrics in Sweden, express his innermost wishes in a clear and farsighted manner. These wishes are, however, only now gradually being realized in this country.

As the importance of allowing paediatricians to take care of premature infants in good time has now been realized, a survey of the occurrence of prematurity is of interest to them. Judging from the information that has been received from different parts of the world, this seems to be somewhat variable. One might even expect to find varyingly high frequencies in different parts of one and the same country as, for instance, Sweden, which, both geographically and from the point of view of its inhabitants, is so different.

Object of the Investigation. The object of this investigation is to give an account of the frequency of premature infants in a

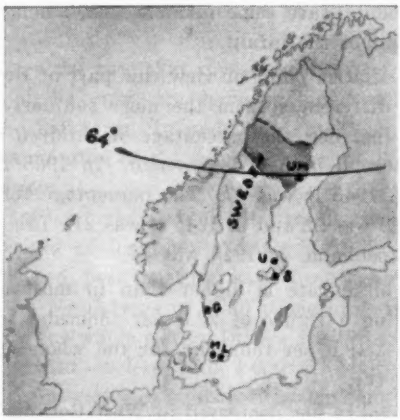

Fig. 1. Scandinavia.
(UM = Umeå. U = Uppsala. S = Stockholm. G = Gothenburg. M = Malmö. L = Lund. Shaded section = West Bothnia.)

northerly part of Sweden, having special regard to any variation in the frequency during the different months of the year. In this connection the distribution of birth weight per month for all the children in the series was investigated.

Place of the Investigation. The series of cases was collected from the Maternity Department of the General Hospital, Umeå, a town in the county of West Bothnia lying in a northerly part of Sweden (64° latitude, see Fig. 1).

Table 1

Approximate length of day in hours during different months of year in Umeå district (64° latitude).

Jan.	Feb.	March	April	May	June	July	Aug.	Sept.	Oct.	Nov.	Dec.
4	7	10	13	17	20	20	18	14	11	8	5

From a paediatric point of view the winter half-year in this part is less beneficial because of the shortness of the days and the low altitude of the sun (see Table 1). It is conceivable that this

circumstance could have some influence on, among other things, the birth weight of the infant.

From a paediatric point of view this part of Sweden presents certain other differences from the more southerly parts of the country. For instance, the percentage of children under the age of 15 is the second highest in Sweden. In 1935 the percentage was 29 and in 1945 it was 27. The percentage for the whole of Sweden in 1935 was 22 and in 1945 it was 21. The percentage for the capital, Stockholm, in 1945 was 17.

Even the birth rate is higher than in most other parts of Sweden, showing a figure of 22.3 per thousand inhabitants for 1945 as against 19.6 per thousand for the whole of the kingdom for the same year.

Infant mortality has decreased in West Bothnia during recent years, as it has also done in other parts of Sweden. Nevertheless it is still the second highest in the country. During the periods 1931—1935 and 1941—1945 it averaged 6.6 % and 3.8 %, respectively. The figures for the whole of Sweden during the period 1941—1945 showed an average of 3.1 %.

The circumstances mentioned above indicate that an investigation of the condition of newborn infants in a district belonging to this part of Sweden ought to be of especial interest.

The Paediatric Department of the General Hospital in Umeå, West Bothnia, was established in 1938 and was one of the first to be instituted outside the larger Swedish cities. This means that paediatric science has been in close cooperation with the Maternity Department of the hospital ever since 1938. It has therefore occurred to us that it would be interesting to investigate the records concerning the frequency of prematurity during the 10 year period 1938—1947.

Material. The investigation is based upon the records of those children who were born in the Maternity Department of the General Hospital in Umeå during the years 1938—1947. This department receives patients from the town of Umeå and the neighbouring villages situated within a radius of about 60 miles. The material comprises all social groups and deals mainly with

the population residing permanently in the county of West Bothnia.

As it is a general rule that investigations of a similar nature concern live births only, we have included only these, both prematures and full term. In each individual case we have made a thorough examination of the information contained in the medical history sheets.

The term »premature» as used here means those infants having a birth weight of less than 2 500 g. All live-born children who have breathed post partum have been included (in compliance with the regulations of 1940 concerning the registration of children). In the whole material there are 13 live-born children with a birth weight of less than 1 000 g. Malformed children falling under the category of monstrosities have not been included.

Information From Other Parts of Sweden. Information about the frequency of prematurity among the children born in Maternity Hospitals exists in many places within and outside Sweden. In this connection we wish to deal only with some comparative facts from Swedish sources. The following information, which is taken in order moving from the south northwards, gives the number of live-born prematures in percentage of the number of live births (according to von Sydow).

Table 2

Frequency of prematurity based on investigations made at some Swedish Maternity Hospitals (Fig. 1).

Lund (town)	1900—1928	(Löfqvist)	6.6 %
Malmö (town).....	1938	(Thorén)	7.6 »
Malmö (town).....	1941	(Thorén)	6.0 »
Gothenburg (town).....	1940	(von Sydow)	5.0 »
Stockholm (town).....	1914—1923	(Lichtenstein)	7.7 »
Stockholm (town).....	1936—1938	(Lichtenstein)	6.2 »
Uppsala (town)	1924—1930	(von Sydow)	6.6 »

Frequency of Prematurity in This Investigation. Our investigation comprises a total of 8 284 live-born infants (4 292 males and 3 992 females — correlation of sexes male/female =107/100).

The total number of prematures was 466 (232 male and 234 female). Thus the frequency of prematurity in this material was 5.6 ± 0.3 %.

Thus one finds that on the whole this figure corresponds to the figures given in comparative material emanating from other parts of the country.

At all events it is evident that the frequency of premature infants in this northerly part of Sweden and its receiving district is not greater than in other parts of the country. Early mortality among the prematures was 21 %.

Distribution of Premature Infants During the Different Months of the Year. The great difference, from a meteorologic point of view, between the winter and summer months in the northern part of Sweden, especially when compared with the southern part of the country, has interested us in investigating the distribution of premature infants throughout the various months of the year. In view of the above-mentioned difference in the length of the days, we came to the conclusion that it was not entirely improbable that one might trace a predominancy in the number of prematures born during the winter half-year, which, from the point of view of health, is probably less beneficial to the pregnant mother. The result of such an investigation will be seen in Table 3 below, in which the number of prematures is given in percentage.

Table 3

Distribution per cent and per month of all premature infants (upper line), non-multiple prematures (middle line), and all children having birth weighte of less than 3 000 g (lower line).

Month	Jan.	Feb.	March	April	May	June	July	Aug.	Sept.	Oct.	Nov.	Dec.
Premature %	7.0	6.0	4.9	4.9	6.6	6.5	6.9	5.8	3.4	4.6	6.3	4.7
Premature (not multiple) %	5.3	4.0	4.0	3.9	4.4	5.6	5.8	4.3	2.9	3.8	4.3	4.1
Total Under 3 000 g %	20.0	15.1	16.7	16.8	19.2	18.0	20.0	17.9	14.1	15.7	17.4	14.2

Fig. 2.

Percentage of: I = all prematures;
II = all prematures except multiple births;
III = all children with a birth weight of less than 3 000 g (with regard to this curve figures 0–9 should read 10–19);
IV = total number of deliveries.

of the total number of children born during the different months of the year (see Fig. 2).

It will be seen from this table together with Fig. 2 that our material shows a considerable difference as regards the distribution of prematures during the different months of the year. Our material is not so great, however, that one can say from it that the difference is statistically certain other than as regards the greatest variations. Nevertheless these variations would indicate, with a fairly high degree of certainty, that there is a certain tendency in the distribution. It may therefore be pointed out that the number of prematures in our material was not noticeably greater during the winter months only, less favourable though these are from the point of view of health. On the other hand, one finds an increased number of prematures during both mid-winter and mid-summer (Fig. 2, Curve 1).

The Number of Twins in the Premature Material. Twins and other multiple births form not a small part of the prematures. Different series of cases give varyingly high multiple frequencies varying from 6 % to over 20 %. No triplets occur in our material. The twin frequency was 24 %.

If one deducts this 24 % (111 cases), there are 355 prematures remaining. It can then be of value to study the distribution of

these prematures proper during the different months of the year in comparison with the figures given above. If we look at the middle line of Table 3 and Curve II in Fig. 2, it will be seen that, even according to this calculation, there is an apparent difference between the different months. In every respect the distribution follows that which appeared in the whole of the premature material and shows an increase during mid-winter and summer.

Investigation of the Frequency of Infants Having a Birth Weight of Less Than 3 000 g. There is reason to suppose that the distribution of the prematures over the different months of the year as indicated in Table 3 and Fig. 2 might be reflected even if one included a somewhat higher weight group. This proved to be the case. We have included all infants having a birth weight of less than 3 000 g (1 415 infants in all). One can even notice a certain accumulation of frequency for the whole of this group during mid-winter and summer (see Table 3, lower line, and Fig. 2, Curve III).

Total Delivery Frequency During the Different Months of the Year. The percentage of variation in the premature frequency during the different months of the year which has been indicated above might possibly be thought to vary in connection with the increase or decrease in the total number of deliveries during the different months of the year. Table 4, below, gives the total number of deliveries during the whole year for our material expressed in percentage of the total number of deliveries during the whole period of our investigation. On the whole, these figures coincide with those sent in from other investigations with regard to the distribution of deliveries during the different months of the year (the State Official Report 1945: 50).

Table 4

Number of deliveries during different months of year expressed in percentage of total number of deliveries.

Jan.	Feb.	March	April	May	June	July	Aug.	Sept.	Oct.	Nov.	Dec.
7.7	6.6	8.9	9.5	9.5	8.7	8.7	8.4	8.9	7.8	7.5	8.0

If this distribution of the total number of deliveries (Fig. 2, Curve IV) is compared with the occurrence of prematures (Fig. 2, Curves I & II), it is evident that the frequency of prematures in our material does not increase in connection with the fact that the total number of deliveries increases during a certain part of the year.

Determination of the Birth Weights During the Different Months of the Year. We found it especially interesting to investigate the average birth weights of the whole of our material during the different months of the year. It might be thought that the winter months, which have short days and are less beneficial to health, might have a deteriorating effect upon the birth weights of infants born during that time. It has not been possible, however, to prove any such difference. All birth weights which have been calculated in averages and for each separate month have shown exceptionally great similarity (see Table 5).

Table 5

Average of all birth weights in our material for each month.

Month	Jan.	Feb.	March	April	May	June	July	Aug.	Sept.	Oct.	Nov.	Dec.
Kg	3.40	3.41	3.44	3.44	3.44	3.41	3.36	3.41	3.46	3.43	3.45	3.44

Summary

An investigation of the distribution of the birth weights per month in a material comprising 8 284 children born during a 10 year period in the Maternity Department of a General Hospital in a northerly part of Sweden (latitude 64°) is reported.

The meteorological conditions with short days during the winter which are less suitable from the point of view of health might be thought to have an influence on the birth weight of infants. This supposition proved to be groundless. The birth weights remained rather constant, being on an average about 3.4 kg for each month during the whole year.

The premature frequency in this material was 5.6 %, which,

on the whole, coincides with information received from other parts of Sweden concerning similar series of cases.

On the other hand, a closer analysis of the distribution of prematures during the different months of the year shows, with a rather high degree of probability, an accumulation during mid-winter and mid-summer. The same type of distribution of birth weights can also be proved if one includes in such calculations all infants having a birth weight of under 3 000 g.

Résumé

Une investigation sur la distribution des poids à la naissance, par mois, chez 8 284 enfants nés pendant une période de 10 ans dans le Département de la Maternité d'un hôpital général d'une région du nord de la Suède (latitude 64°).

Les conditions météorologiques (journées d'hiver courtes) qui, au point de vue de la santé, sont moins favorables, peuvent avoir une influence sur le poids de l'enfant à la naisssance. Néanmoins, cette théorie s'est révélée sans fondements. Le poids à la naissance reste assez constant, étant d'une moyenne d'environ 3.4 kg pour chaque mois de l'année.

La fréquence des naissances avant terme offerte par ce matériel était de 5.6 %, ce qui coincide avec l'information concernant les mêmes matériels reçus d'autres régions de la Suède.

D'un autre côté, une analyse plus détaillée de la distribution des enfants nés avant terme pendant les divers mois de l'année manifeste avec une assez grande probabilité la fréquence de ces naissances au cours de la mi-hiver et de la mi-été. Le même type de distribution de poids à la naissance peut être montré, si l'on comprend dans des calculs de ce genre tous les enfants ayant un poids inférieur à 3 000 grammes.

Zusammenfassung

Eine Untersuchung der Verteilung des Geburtsgewichts pro Monat an 8 284 Kindern, die im Verlauf von zehn Jahren in der Entbindungsanstalt eines Krankenhauses im nördlichen Schweden (64. Breitengrad) geboren waren.

Es könnte scheinen, als ob die meteorologischen Bedingungen mit kurzen Tagen in der Winterzeit, vom Standpunkt der Gesundheit her, weniger günstig sind und so einen Einfluss auf das Geburtsgewicht des Kindes ausüben könnten. Eine solche Theorie hat sich jedoch als haltlos erwiesen. Das Geburtsgewicht hat sich vielmehr als konstant gezeigt, und zwar im Durchschnitt etwa 3.4 kg für jeden Monat des ganzen Jahres.

Die Häufigkeit der Frühgeburten an diesem Material war 5.6 %, was im ganzen mit den Angaben über ähnliches Material aus anderen Teilen Schwedens übereinstimmt.

Andererseits zeigt eine genauere Analyse der Verteilung von Frühgeburten über die verschiedenen Monate des Jahres mit dem Anspruch auf eine weit grössere Wahrscheinlichkeit eine Steigerung zur Zeit der winterlichen und sommerlichen Sonnenwende. Derselbe Typ der Verteilung des Geburtsgewichts kann auch erkannt werden, wenn man in solche Berechnungen alle Säuglinge einschliesst, deren Geburtsgewicht unter 3 000 g beträgt.

Sumario

Se ha efectuado una investigación de la distribución del peso de nacimiento por mes, utilizando un material de 8 284 niños nacidos durante un período de 10 años en el departamento de Maternidad de un Hospital General en el norte de Suecia (latitud 64°).

Las condiciones meteorológicas con días cortos durante el invierno, los cuales desde el punto de vista sanitario son menos convenientes, se pensaba que tenían una influencia sobre el peso de nacimiento del niño. Esta teoría, sin embargo, se comprobó que carecía de fundamento. El peso de nacimiento ha permanecido bastante constante y ha sido de aproximadamente 3.4 kilos durante cada mes en todo el año.

Le frecuencia de prematuros ha sido de 5.6 %, lo cual, en general, coincide con las informaciones recibidas de otras partes de Suecia.

Por el otro lado, un análisis detallado de la distribución de los prematuros durante los diferentes meses, con alto grado de probabilidad, muestra una indicación de acumulación durante el

solsticio estival y hiemal. El mismo tipo de distribución de pesos de nacimiento se puede comprobar también si, en esta clase de cálculos, se incluye a todos los niños que tienen un peso de nacimiento de menos de 3 000 gramos.

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Studien über die Antihistaminwirkung an der menschlichen Haut

von

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Bereits früher haben wir darauf hingewiesen (P. Kallós und L. Kallós-Deffner, 1, 2), dass das Studium der »triple response» von Th. Lewis, wie sie nach Histaminapplikation an der Haut zu beobachten ist, ein geeignetes Objekt zur Messung der gegen Histamin antagonistischen Wirkung verschiedener Pharmaka darstellt. Durch planimetrische Ausmessung der Fläche der Histaminreaktion konnten wir dabei zeigen, dass die intrakutane Einspritzung von 0.1 ml Histaminlösung 10^{-5} (alle Konzentrationsangaben beziehen sich auf basisches Histamin) bei unvorbehandelten Versuchspersonen eine Reaktion von 25.35 ± 0.69 qcm hervorruft und dass ein wirksamer Histaminantagonist, nämlich 2-(N-phenyl-N-benzyl-aminomethyl)-imidazolin[1] in entsprechenden Konzentrationen im Stande ist diese Reaktion erheblich zu vermindern. Bei Einspritzung eines Gemisches von Histamin und Antistin verminderte sich die Fläche der Hautreaktion um 88.9 ± 1.4 % und betrug somit nur 2.82 ± 0.35 qcm. Bei intramuskulärer bzw. peroraler Anwendung geeigneter Antistinmengen erhielten wir ebenfalls eine deutliche Hemmung der Histaminhautreaktion. Im ersteren Falle verminderte sich die Fläche der Reaktion um 47.9 ± 2.3 % und betrug somit 13.21 ± 0.46 qcm, im letzteren Falle um 31.0 ± 3.1 % und betrug somit 17.48 ± 0.63 qcm. Alle Werte bzw. Differenzen sind statistisch sichergestellt. Nach Veröffentlichung dieser Untersuchungen

[1] »Antistin-Ciba». Für die Überlassung von Versuchsmengen von Antistin danken wir der Ciba A.G., besonders Herrn Prof. R. Meier, Basel, verbindlichst.

kam uns eine vorläufige Mitteilung von M. D. LEAVITT und CH. F. CODE zur Kenntnis, die mit einer im Prinzip gleichartigen Methode vollständig mit den unsrigen übereinstimmende Resultate erhalten haben, wobei sie einen anderen Histaminantagonisten, nämlich Beta-dimethylaminoethyl-Benzhydrilaether-Hydrochlorid (»Benadryl«), angewandt haben. Vergleichshalber führen wir einige von den genannten Autoren ermittelte Werte an. Die Fläche der Histaminhautreaktion bei unvorbehandelten Versuchspersonen betrug nach diesen Autoren 16—25 qcm. Durch lokale Applikation von Benadryl konnte die Fläche um 61.6 %, durch intravenöse Injektion von Benadryl um 51.7 % und durch perorale Benadrylgaben um 33 % vermindert werden. Da eine statistische Auswertung in der vorläufigen Mitteilung der Autoren nicht enthalten ist, können die Werte nicht direkt mit den unsrigen verglichen werden, sie zeigen aber immerhin eine weitgehende Übereinstimmung. Es sei hierbei erwähnt, dass die Untersuchungen von M. D. LEAVITT und CH. F. CODE dadurch kompliziert worden sind, dass Benadryl bei lokaler Applikation in der Haut einerseits eine anaesthetische Wirkung entfaltet und andererseits auch eine lokale Reizwirkung ausübt. Das von uns angewandte Antistin ist in der notwendigen Konzentration (meistens 2×10^{-4}) von diesen Nebenwirkungen völlig frei (vgl. hierzu R. MEIER und K. BUCHER). S. FRIEDLAENDER und S. M. FEINBERG sind zu ähnlichen Feststellungen gekommen, sie haben aber die Intensität der Histamin-Hautreaktion subjektiv beurteilt. Jedenfalls geht auch aus ihren Untersuchungen deutlich hervor, dass Benadryl besonders bei lokaler Anwendung die Histamin-Hautreaktion deutlich hemmt. Dasselbe gilt für ein drittes sehr aktives Antihistaminikum, nämlich für das Pyridil-N'benzyl-N-dimethylethylendiamin (»Pyribenzamin«). Darüber hinaus konnten S. FRIEDLAENDER und S. M. FEINBERG an der menschlichen Haut auch zeigen, dass allergische Hautreaktionen durch Benadryl bzw. Pyribenzamin in völlig entsprechender Weise gehemmt werden.

Es dürfte von vorne herein klar sein, dass die Einwirkung von Histamin nicht nur den Tonus, sondern auch die Funktion der reagierenden Gefässe beeinträchtigt. Untersuchungen, welche

beweisen dass Histamin eine Erhöhung der Gefässpermeabilität bewirkt, sind zahlreich (vgl. z. B. H. GADDUM). Wir haben früher (P. KALLÓS und L. KALLÓS-DEFFNER, 3) für gewisse Formen der allergischen Reaktion an der Meerschweinchenhaut Ähnliches zeigen können. Dabei ermittelten wir die Kongorotpermeabilität der betroffenen Gefässe. Ähnliche Untersuchungen wurden auch mit Histaminantagonisten mehrfach vorgenommen. F. B. TRAUB, U. FRIEDEMANN und D. LANDSTADT haben somit zeigen können, dass die Permeabilität der Hautkapillaren von Kaninchen durch intrakutane Applikation von Histamin erheblich erhöht wird, so dass intravenös zugeführtes Diphtherieantitoxin in mit Histamin vorbehandelten Hautstellen in grösserer Menge nachgewiesen werden kann. M. R. LAST und E. R. LOEW sind mit der Trypanblaumethode (Trypanblau wird intravenös zugeführt und in der Haut durch seine Farbe nachgewiesen) an der Kaninchenhaut zu gleichen Ergebnissen gekommen. Darüber hinaus konnten sowohl F. B. TRAUB als auch M. R. LAST und deren Mitarbeiter zeigen, dass Benadryl die permeabilitätssteigernde Wirkung von Histamin antagonistisch beeinflusst. M. R. LAST und E. R. LOEW haben auch Versuche über die Beeinflussung einer allergischen Reaktion, nämlich des Arthus-Phänomens, durch Benadryl vorgenommen, und zwar an der Haut von für Pferdeserum allergischen Kaninchen. Das Arthus-Phänomen konnte nur unerheblich durch Benadryl gehemmt werden. Es dürfte allerdings von vorne herein nicht zu erwarten gewesen sein, dass gerade das Arthus-Phänomen durch Histaminantagonisten beeinflusst werden kann (Lit. bei R. MEIER und K. BUCHER). Dies erwähnen auch die Autoren selbst. Man sollte vielmehr Hautreaktionen wählen, die wenigstens während eines begrenzten Zeitraumes identisch mit einer Histamin-Hautreaktion verlaufen und von denen es daher anzunehmen ist, dass bei ihrer Entstehung Histamin eine Rolle spielt. Von den allergischen Hautreaktionen dürfte daher die sog. urtikarielle Sofortreaktion ein geeignetes Versuchsobjekt darstellen.

Wir haben uns die Frage gestellt, inwieweit eine permeabilitätssteigernde Wirkung von Histamin an der menschlichen Haut nachgewiesen werden kann und inwieweit bei allergischen, ur-

tikariellen Reaktionen analoge Verhältnisse vorliegen. Es war zu erwarten, dass beide Reaktionsarten mit einer Steigerung der Permeabilität der reagierenden Gefässe einhergehen und daher sollte auch die Beeinflussung der Verhältnisse durch Antistin, dessen histaminantagonistische Wirkung wir an der menschlichen Haut bereits früher festgestellt haben, untersucht werden. Seit den Untersuchungen von K. LANGE und Mitarbeitern (1, 2, 3, 4) war es bekannt, dass Fluoresceinnatrium zur Durchführung derartiger Untersuchungen besonders geeignet ist. Auch kleine Mengen dieses Farbstoffes können durch ihre Fluoreszenz im Ultraviolettlicht (Wellenlänge 3 650 Å) in der Haut leicht nachgewiesen werden.[1] Nach eingehenden Voruntersuchungen, die hier nicht berücksichtigt werden sollen, haben wir die Methode gewählt, die Zeit zu bestimmen, welche zum Verschwinden der Fluoreszenz einer Hautquaddel notwendig ist, die intrakutan unter einheitlichen Bedingungen mit 0.05 ml einer Fluoresceinnatriumlösung in der Konzentration von 2×10^{-5} bei erwachsenen Versuchspersonen gesetzt wurde. In allen Versuchen wurden am rechten bzw. linken Vorderarm der Versuchspersonen je zwei Quaddeln gesetzt, wobei immer die proximale Quaddel des re. Armes mit der distalen des li. Armes korrespondierte und umgekehrt. Alle Ablesungen wurden von zwei Untersuchern unabhängig voneinander vorgenommen und alle Werte statistisch behandelt.[2] Jede Versuchsgruppe enthielt 20 Versuchspersonen, so dass jeweils wenigstens 40 identische Quaddeln zur Auswertung gelangten.

In erster Linie ermittelten wir die Fluoreszenzzeit bei unvorbehandelten Versuchspersonen, und zwar bei gesunden Erwachsenen. Die Fluoreszenzzeit beträgt unter den vorher genannten Bedingungen 33.30 ± 1.25 Minuten ($\sigma = \pm 5.59$ Min.). Bei denselben Versuchspersonen wurde dann die Fluoreszenzzeit unter den gleichen Bedingungen bestimmt, jedoch mit dem Unterschied, dass das Fluoresceinnatrium in einer Histaminlösung von der

[1] Wir haben die Ultraviolettlampe Modell HGU der Luma A.G., Stockholm, angewandt.

[2] Für die statistische Bearbeitung unseres Materials möchten wir Herrn Prof. GUNNAR DAHLBERG (Uppsala) wärmstens danken.

Konzentration 10^{-5} gelöst wurde. Dabei betrug die Fluoreszenzzeit 7.25 ± 0.49 Minuten ($\sigma = \pm 2.20$). Die Differenz zwischen diesen beiden Werten beträgt 26.05 ± 1.34 Minuten und ist somit statistisch sichergestellt. In der nächsten Versuchsreihe haben wir ausser Histamin (10^{-5}) auch Antistin in der Konzentration 2×10^{-4} zugesetzt. In diesem Falle betrug die Fluoreszenzzeit 34.15 ± 1.11 Minuten ($\sigma = \pm 4.96$). Eine Differenz zwischen der normalen und dieser Fluoreszenzzeit besteht somit nicht, mit anderen Worten das Antistin hat die Histaminwirkung völlig aufgehoben.

Die zweite Versuchsgruppe bestand aus 20 erwachsenen Asthmapatienten, die sämtlich für Hausstaub allergisch waren, nicht aber für Weizenmehl. Bei diesen Patienten wurde im anfallsfreien Zustand erstens die normale Fluoreszenzzeit bestimmt, welche 34.70 ± 1.27 Minuten ($\sigma = \pm 5.69$) betrug und somit mit der bei der ersten Gruppe ermittelten Zeit völlig übereinstimmte. Der Zusatz von Histamin (10^{-5}) setzte die Fluoreszenzzeit auf 7.10 ± 0.60 Minuten ($\sigma = \pm 2.67$) herab. Die Permeabilitätssteigerung, welche hierin zum Ausdruck kommt, ist mit derjenigen, die unter den gleichen Bedingungen bei Gesunden auftritt, völlig übereinstimmend. Zusatz von Antistin (2×10^{-4}) stellte auch in dieser Gruppe die normale Fluoreszenzzeit wieder her, indem diese 34.20 ± 1.06 Minuten ($\sigma = \pm 4.75$) betrug. Auch diesbezüglich ist die Übereinstimmung mit der vorigen Gruppe eine vollständige. Gesunde Versuchspersonen und Asthmapatienten im anfallsfreien Zustand verhalten sich also diesbezüglich völlig gleich.

Bei den Asthmapatienten wurde dann der Einfluss von Allergenextrakt auf die Fluoreszenzzeit ermittelt, und zwar in der Weise, dass zu der Fluoreszeinlösung Allergen in der Menge zugesetzt wurde, welche gerade eine deutliche urtikarielle Hautreaktion bei positiv reagierenden Allergikern zu erzeugen im Stande war.[1] Alle 20 Asthmapatienten konnten erstens mit einem Allergen, für welches sie stark allergisch waren, nämlich Hausstaub, und zweitens mit einem Allergen, welches bei ihnen

[1] Für die Überlassung der titrierten Allergenextrakte danken wir der A.G. Hässle-Tika, Hässleholm.

keine Reaktion hervorzurufen im Stande war, nämlich Weizenmehl, geprüft werden. Dabei erwies sich, dass die Fluoreszenzzeit in der stark reagierenden, mit Hausstaub beschickten Hautstelle stark herabgesetzt war und nur 5.70 ± 0.50 Minuten betrug ($\sigma = \pm 2.23$). Die Differenz zwischen diesem Wert und dem Normalwert der Gruppe beträgt somit 29 ± 1.10 Minuten und ist statistisch sichergestellt. Die Herabsetzung der Fluoreszenzzeit übertrifft sogar die durch Histamin hervorgerufene, was durch quantitative Unterschiede erklärt werden dürfte und hier nicht näher diskutiert werden soll. Weizenmehlextrakt, der bei diesen Patienten, wie erwähnt, keine urtikarielle Reaktion bedingte, hat die Fluoreszenzzeit unter denselben Bedingungen überhaupt nicht beeinflusst, vielmehr wiesen die Hautstellen eine mit der normalen völlig übereinstimmende Fluoreszenzzeit von 34 Minuten auf. Nun wurden bei denselben Patienten 40 Hautstellen mit einer Lösung beschickt, die ausser Fluorescein und Hausstaubextrakt (in der gleichen Konzentration wie in den vorerwähnten Versuchen) auch Antistin in der Konzentration von 2×10^{-4} enthielt. Hierbei wurde eine Fluoreszenzzeit von 34.75 ± 0.98 Minuten ($\sigma = \pm 4.40$) ermittelt. Diese Fluoreszenzzeit stimmt mit der normalen überein, somit hebt Antistin unter den genannten Bedingungen die Wirkung des spezifischen Allergens auf die Haut völlig auf. Histamin-Hautreaktion und allergisch-urtikarielle Reaktion verhalten sich somit unter den hier genannten Bedingungen identisch.

Ergänzend soll erwähnt werden, dass wir dieselben Versuche bei einer kleinen — nur aus 5 Versuchspersonen bestehenden — Gruppe von Bäckern, die sämtlich für Weizenmehl, nicht aber für Hausstaub allergisch waren, wiederholt haben. Dabei ergab sich, dass Weizenmehlextrakt, der nun positive Reaktionen hervorrief, die Fluoreszenzzeit stark herabsetzte, während Hausstaubextrakt sie unbeeinflusst liess. Antistin hob die Weizenmehlwirkung ebenso auf, wie die Hausstaubwirkung bei der vorerwähnten Versuchsgruppe. Diese Gruppe ist zu klein, um statistisch ausgewertet zu werden.

Zusammenfassung

Mit Hilfe der Bestimmung der Resorptionszeit von intrakutan eingeführtem Fluoresceinnatrium konnte gezeigt werden, dass Histamin-Hautreaktionen und allergisch-urtikarielle Reaktionen in gleichartiger Weise mit einer erheblichen Erhöhung der Permeabilität der reagierenden Gefässe einhergehen und dass diese Permeabilitätssteigerung durch Histaminantagonisten (Antistin) unter geeigneten quantitativen Bedingungen in beiden Fällen völlig gehemmt werden kann. Die Methode gibt Werte, welche sich zur mathematischen Behandlung gut eignen und somit quantitative Untersuchungen über die Wirkung von Histaminantagonisten erlauben.

Summary

The resorption rate of intracutaneously injected sodium fluorescein is distinctly increased in the area of histamine and urticarial (allergic) skin reactions. The permeability of the capillaries in both of these types of wheals is markedly increased. This increase of permeability was under certain quantitative circumstances reduced or inhibited by a potent antihistaminic drug, Antistine. The estimation of the resorption rate of sodium fluorescein give values which make a quantitative evaluation of the effectivity of antihistaminic drugs possible.

Résumé

Grâce à la détermination du temps d'absorption de la fluorescéine sodée injectée sous la peau, il a été possible de démontrer que les réactions de la peau à l'histamine et les réactions allergiques-urticariennes se passent de manière semblable: élévation considérable de la perméabilité des vaisseaux réagissants. On a encore démontré de la même manière que cette augmentation de perméabilité peut être complètement arrêtée dans les deux cas par l'antagoniste de l'histamine (antistine), employé à doses convenables. Cette méthode donne des valeurs qui se prêtent bien à des évaluations mathématiques et permettent ainsi d'étudier les effets produits par les antagonistes de l'histamine.

Sumario

Gracias a la determinación del tiempo de absorción de la fluorecina sodica injectada bajo la piel, ha sido posible demostrar que las reacciones de la piel a la histamina, y las reacciones alergicas urticarianas son semejantes: interviniendo en su producción un aumento considerable de la permeabilidad de los vasos. Se ha podido ademas demostrar de la misma manera, que este aumento de la permeabilidad puede ser completamente detenido en ambos casos por el antagonista de la histamina (antistina) empleada a dosis convenientes. Este metodo, da valores que se prestan bien a evaluciones matematicas y permite de esta manera estudiar los efectos producidos por los antagonistas de la histamina.

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FROM THE PAEDIATRIC CLINIC OF KAROLINSKA INSTITUTET AT THE NORRTULL HOSPITAL, STOCKHOLM.
CHIEF: PROF. A. WALLGREN.

The Significance of Depth of Insertion of the Thermometer for Recording Rectal Temperatures

by

P. KARLBERG

A common and frequently used method of determining the condition of the patient is the measurement of the body temperature. This is not the same over the whole body; in general it is higher the farther in the body it is recorded and also higher in active organs. Here in Sweden, the body temperature is nearly always considered to be that of the rectum. It is measured by inserting a thermometer a certain distance into the rectum. Most rectal thermometers now in use are of special design (see Fig. 1), having a narrower part up to about 3 cm from the point of the quicksilver bulb and then abruptly becoming considerably broader where the thermometer scale itself is fixed. It would seem that those who originally gave the thermometer its form considered a point 3 cm above the sphincter in the ampulla to be a suitable measuring point. However, the broader part of the thermometer constitutes no obstacle to the deeper insertion of the thermometer, except perhaps in the case of infants. The fact that the depth of measurement may vary must therefore be taken into account.

The depth at which the measurement is carried out is not without its significance, as was observed by MONRAD as early as 1903 and by TACHAU in 1912. The latter mentions a difference in temperature of 0.1°—1.7° C between measurements with the thermometer inserted only so far as barely to hide the column of mercury and with the thermometer inserted several centimeters deeper. In 1943 HARRESTRUP ANDERSEN repeated TACHAU's

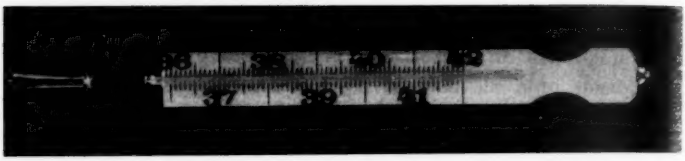

Fig. 1.

measurements in connection with a case of »subfebrility», pyrexia of unknown origin which was treated for from two—three months and was discovered only after a number of examinations and two periods in hospital to be due to the unusually deep insertion of the thermometer. In ten children under six months and ten aged from six—ten years, ANDERSEN determined the difference in rectal temperature in measurements made with the column of mercury barely hidden by the sphincter and with the thermometer inserted up to the 38° C line. Similar investigations were made in the following year, 1944, by WALLDÉN in a Swedish sanatorium, and he also included adults. Their results have been collected in graph form (see Fig. 2). ANDERSEN obtained an average difference of about 1.1°—1.2° C and WALLDÉN of about 0.4°. Both recorded maximum differences of up to 1.8°. Both were able to show that several pyrexial states were occasioned by too deep insertion and they considered that if it were desired to retain 37° C as the upper limit for afebrile states, the thermometer should not be inserted too far and the measurements should be taken at the same depth. The above-mentioned differences of temperature were, however, measured at only two different depths, the outer of which at least was not very exactly defined. Nor has the most suitable depth been stated with any accuracy. In order to be able to determine this more closely and in order to find out to what limits the depth of measurement may be allowed to vary, the present investigations have been carried out.

The temperature of the rectum has been recorded with the thermometer inserted at increasing depths of 1 cm from the outer edge of the sphincter up to a depth of 10 cm in the rectum. For this purpose, two series-connected thermo-elements (copper/constant) embedded in a narrow rubber tube have been used, giving

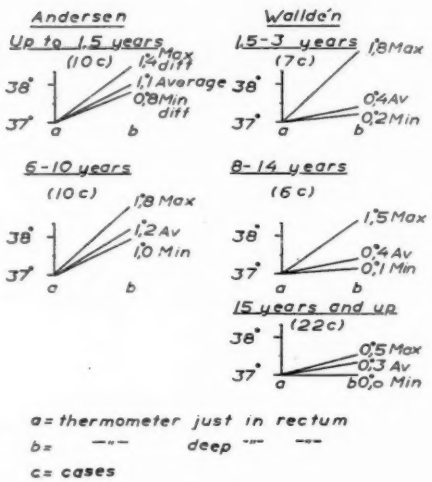

Fig. 2.

readings on a galvanometer with an accuracy of 0.05° C. The temperature rises, as is to be expected, relatively quickly at first and then slowly attains a more constant value. Investigations have been made in this way on children from birth up to fifteen years, and also on a number of adults aged from twenty—thirty years. The results thus obtained have been divided into different weight groups and set out graphically in Fig. 3, with the depth in cm on the abscissa and the temperature difference on the ordinate. All those examined were afebrile according to the usual temperature measurements, for which reason the curves have been arranged under each other without regard to level, since it is the course of the curves according to depth of measurement which is to be illustrated.

As was to be expected, the rise in temperature per cm for all age groups is less the farther the thermometer in inserted in the rectum until a relatively constant temperature is reached. The

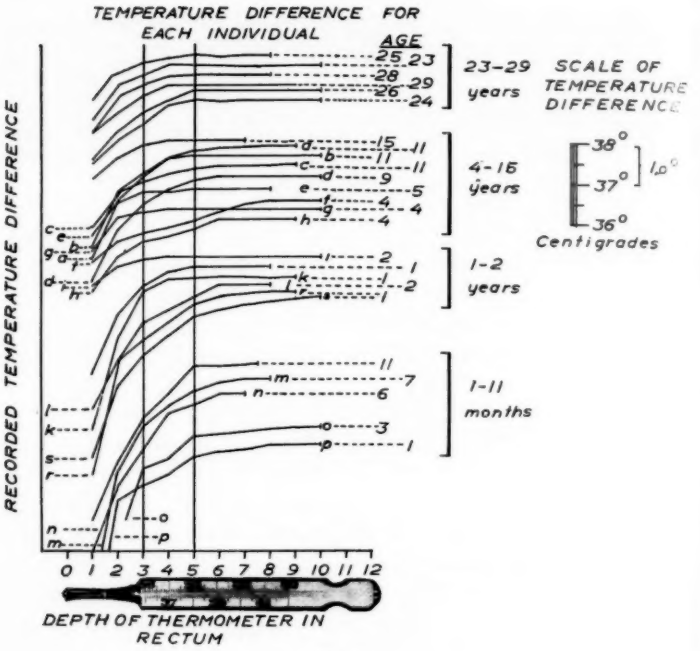

Fig. 3.

steepness of the curves and therefore the depth required to obtain a more constant temperature decreases considerably with increasing age and size. In general, this constant temperature has been reached for all age groups at a depth of about 5 cm (Figs. 3, 4). This depth of measurement is consequently suitable when greater accuracy is required, since a minor variation in depth of measurement produces hardly any measurable difference in temperature. As may be seen from the thermometer inset in the diagram, it is constructed not for this depth but for measurement at a depth of 3 cm. The difference in temperature between a measurement depth of 3 and 5 cm or more varies in adults from 0.1° to 0.4° C, and in older children down to two—three years from 0.6°—0.8°; in infants the variability may be over 1.0°, with,

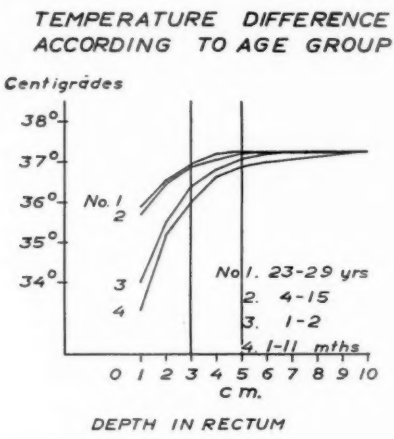

Fig. 4.

however, considerable individual variations. So great a difference as 1.8°, which ANDERSEN and WALLDÉN noted, has not been observed, probably due to the fact that the above differences were reckoned first from a minimum depth of 3 cm. In older children and adults the measurements generally take place, by reason of the construction of the thermometer, at a depth of about 3—4 cm, and the upper limit for normality of 37° C in the morning is valid at this depth. It may happen, however, that the temperature is measured at a greater depth. In *adults* this produces no rise in temperature or at most a rise of some tenths only and this difference will be observed only in sanatoria and other hospitals where accurate recording is of importance (cf. WALLDÉN). In older children the depth of measurement is more important, especially if the child has an anxious and zealous mother whose child must be absolutely »normal» before it is allowed to get up after a feverish illness and who, in order to take the temperature as »properly» as possible, inserts the thermometer up to about half its length (5 cm or more). It is not uncommon either to see children in the outpatient departments who are examined for persistent pyrexia following, for example, an ordinary catarrhal

infection, the true cause of whose pyrexia is too deep insertion of the thermometer in the rectum. In the case of small children and infants, the measuring technique is more uniform, since even a zealous mother must content herself with inserting only that narrower part of the thermometer.

The *practical conclusions* from these observations are therefore as follows.

1. Varying temperatures resulting from different depths of measurement could be avoided if the depth of measurement were fixed at 5 cm or more. This may be difficult to institute, as it must then be realized that the upper limit of the normal should in normal conditions be 37.3°—37.4° C. Furthermore, the risks of damage to the thermometer are increased. The lesser depth is therefore likely to be retained, but it should be fixed at from 3.0—3.5 cm and the significance of the depth of measurement should be made more generally known, perhaps by means of a notice accompanying each new rectal thermometer.

2. In the case, however, of scientific investigations, in which accurate temperature measurements are required in order to record small differences of temperature, the greater depth of 5 cm should be used. (This principle is valid even for measurements on experimental animals.) At depths less than this a difference of about 0.5 cm, which is difficult to avoid, may easily simulate temperature differences of 0.1°—0.2°.

3. In infants, and especially newborn or weak children, it must be realized that the temperature at a depth of 3 cm, as usually taken, is less representative of the average temperature of the body. If in these infants the surrounding temperature is raised so that the rectal temperature is 36.6°—37.0° then the body temperature will be raised to even considerably higher degrees.

Summary

The most suitable depth of measurement for the determination of rectal temperature, and the limits within which it may be allowed to vary, have been determined by thermo-electric methods, the determinations having been made at centimeter intervals from the sphincter edge up to a depth of 10—15 cm. Children aged

from birth up to fifteen years as well as some adults were examined. The requisite depth for reaching a constant temperature decreases with the age of the child; in general, a constant temperature is obtained for all ages at a depth of about 5 cm, with the greatest accuracy in the older ones. Thermometers in current use are constructed for measurement at a depth of 3 cm. The consequences of this are discussed.

Résumé

La meilleur profondeur pour la détermination de la température rectale et les limites entre lesquelles il est permis de varier, ont été déterminées par des méthodes thermo-électriques, les déterminations ayant été faites de cm en cm, à une distance du bord du sphincter allant jusqu'à 10—15 centimètres. Des enfants présentant des bords différents, de la naissance jusqu'à 15 ans, ont été examinés, ainsi que des adultes. La profondeur requise pour atteindre la température constante diminue avec l'âge; en général, une température constante est obtenue, à tous les âges, et avec une parfaite exactitude pour les personnes plus âgées, à une profondeur de 5 cm.

Les thermomètres d'usage courant sont construits pour la mensuration à une profondeur de 3 cm. Les conséquences en sont discutés.

Zusammenfassung

Die Tiefe der Messung zur Bestimmung der Rectaltemperatur und die Grenzen, innerhalb deren eine Änderung zulässig ist, wurden durch thermo-elektrische Methoden bestimmt; hierbei wurden die Messungen ausgeführt im Abstand von je einem Zentimeter, gerechnet vom Rande des Sphinkers bis zu einer Tiefe von 10—15 cm. Kinder verschiedener Altersklassen, von Neugeborenen bis zu 15jährigen wurden untersucht, ebenso einige Erwachsene. Die für das Erreichen einer konstanten Temperatur erforderliche Tiefe nimmt mit dem Alter des Kindes ab. Im Allgemeinen wurde eine konstante Temperatur erhalten bei einer Tiefe von etwa 5 cm, mit der grössten Exaktheit bei den Älteren.

Die gebräuchlichen Thermometer sind konstruiert für das Messen in einer Tiefe von 3 cm. Die Ergebnisse der Untersuchung werden erörtert.

Sumario

La profundidad más conveniente de mediciones para la determinación de la temperatura rectal, y los líquidos dentro de los cuales se puede permitir que varíe, se han determinado mediante métodos termo-eléctricos; se han hecho las determinaciones por cada centímetro de distancia desde el borde del esfinter hasta una profundidad de 10 a 15 cm. Se han examinado tanto niños (de distintas edades, desde el nacimiento hasta la edad de 15 años) como adultos. La profundidad necesaria para obtener una temperatura constante disminuye con la edad del niño; generalmente la temperatura es constante para todas edades a una profundidad aproximada de 5 cm, con mayor exactitud en los de mayor edad. Los termómetros de uso corriente están construídos para medición a una profundidad de 3 cm. Se discuten las consecuencias de esto.

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The Sedimentation Rate in Nursing Mothers

by

FRITZ KARLSTRÖM, Karlstad

Within our own generation light has been thrown on the sedimentation rate (s.r.) by FÅHRÆUS's epoch-making work. The reaction during the puerperium has been studied by BAGER, among others. He found that it was of no practical clinical importance even if for purposes of comparison the value was obtained immediately before delivery. There are very few particulars about the sedimentation reaction immediately after completion of the puerperium. FÅHRÆUS states that in nineteen women the average figure for the s.r. during the first month after partus was 41 mm and during the second month 19.5 mm. VOGT found the mean s.r. to be 25.5 mm on the seventh day after partus and 12.0 six weeks afterwards. I have found no systematic investigation in the literature of the reaction throughout the whole nursing period. Yet it may be of practical importance particularly for children's doctors, who have often not only to watch over the child but also over the mother during the lactation period, to know how the s.r. falls during the months after confinement.

To endeavour to ascertain this I made the following investigation.

During the latter part of the year 1945 and the years 1946 and 1947 the s.r. of the nursing mothers in the Children's Department of the Karlstad Hospital was taken once a week. The mothers who had been ill during any part of their stay in hospital were excluded from the series. In order to make doubly sure that the mothers had not suffered from any slight infectious illnesses which might infect their children, those whose children had had temperatures during their stay in hospital were also

Table I

The s.r. in mothers at different times after partus.

Time After Partus	No.	$M \pm \varepsilon(M)$	σ
2nd Week	40	25.1±2.2	13.8
3rd »	60	19.4±1.4	10.9
4th »	72	14.4±1.2	10.2
2nd Month	229	13.1±0.6	9.0
3rd »	52	11.9±1.3	9.7
4th »	35	10.7±1.0	5.9
5th »	20	9.3±0.9	4.2
6th »	20	10.3±1.9	8.7

excluded from the series. The s.r. was determined according to WESTERGREN's method and the readings-off took place after one hour and two hours. In the statistical treatment only the figure for the one hour value was included.[1] After elimination in this manner the material comprised 168 mothers, of whom 51 were the mothers of premature and 117 of full-term children. The number of s.r.'s taken was 528.

The results appear from Table I. As will be seen, *during the time immediately after partus the s.r. is considerably raised. It falls rapidly during the first month, then more slowly, and not until after the fourth month does it reach the upper limit of the normal.* According to DAHLBERG the normal value for women is average = 8.1 mm and $\sigma = 6.3$ mm. The variation range is large at first but gradually becomes normal.

It is conceivable that there is some difference between the s.r. of mothers with premature children and that of mothers with full-term children, especially during the period immediately after partus. To investigate this I collocated the numerical material in large groups and calculated the difference between them, as shown in Table II.

It appears from the table that during the first month there is no difference between the two groups, *but during the second,*

[1] I owe a debt of gratitude to Professor G. DAHLBERG, Uppsala, for the statistical treatment.

Table II

The s.r. of mothers of premature children and that of the mothers of full-term children.

	Mothers With						Diff.
	Premature Children			Full-Term Children			
	No.	$M \pm \varepsilon(M)$	σ	No.	$M \pm \varepsilon(M)$	σ	
1st Month	93	18.99±1.31	12.62	79	18.23±1.28	11.35	0.76±1.83
2nd »	94	14.94±1.06	10.29	135	11.74±0.66	7.65	*3.20±1.25*
3rd+4th »	10	22.80±4.79	15.14	77	9.94±0.65	5.73	*12.86±4.83*
5th+6th »	9	7.22 —	—	31	10.52±1.34	7.46	

Table III

The s.r. of mothers whose children received breast milk only and that of mothers whose children received mixed nutriment.

	Mothers Whose Children Received						Diff.
	Breast Milk Only			Mixed Nutriment			
	No.	$M \pm \varepsilon(M)$	σ	No.	$M \pm \varepsilon(M)$	σ	
1st Month	154	18.42±0.98	12.12	18	20.50±2.76	11.70	−2.08±2.93
2nd »	187	13.18±0.64	8.69	42	12.50±1.58	10.23	0.68±1.70
3rd+4th »	60	12.00±1.22	9.45	27	10.11±0.95	4.93	1.89±1.55
5th+6th »	16	7.44±1.03	4.13	24	11.33±1.57	7.71	−3.89±1.88

third, and fourth months after partus the s.r. of mothers of premature children is probably higher than that of mothers of full-term children.

Whether the secretion of breast milk in itself plays any part in the s.r. could best be discovered by comparing the s.r. of nursing mothers with that of non-nursing mothers. I had not a sufficiently large series of the latter at my disposal, however. Therefore I have compared the s.r. of mothers who breast-fed their children entirely with the s.r. of mothers whose breast milk was sufficient for only half or less of their children's nutriment. The result appears from Table III.

The table shows that there is *no verified difference between the s.r. of mothers whose children receive mixed nutriment and the s.r. of mothers who breast-feed their children entirely.*

Summary

The sedimentation rate of 168 healthy nursing mothers was taken 528 times during different phases of the nursing period. Immediately after delivery it was considerably elevated. Thereafter it sank rapidly during the first month, then more slowly, but did not reach the upper limit of the normal until after four months.

During the second, third, and fourth months after delivery the sedimentation rate of the mothers of premature children is probably higher than that of the mothers of full-term children.

No definite difference has been established between the sedimentation rate in mothers who breast-feed their children entirely and those who give them supplementary formula feedings.

Résumé

La vitesse de sédimentation de 168 mères allaitant fut mesurée 528 fois, et au cours des différentes phases de la période d'allaitement. Immédiatement après l'accouchement, elle était considérablement élevée. Puis elle s'abaissa rapidement durant le premier mois, puis plus lentement, mais n'atteignait pas encore la limite supérieure de la normale après quatre mois. Durant les deuxième, troisième et quatrième mois après l'accouchement, la vitesse de sédimentation des mères d'enfants nés avant terme est probablement plus élevée que celle des mères d'enfants nés à terme.

On n'a établi aucune différence entre la vitesse de sédimentation des mères nourrissant entièrement leurs enfants au sein et de celles qui font un allaitement mixte.

Zusammenfassung

Bei 168 gesunden stillenden Müttern wurde die Blutsenkungsreaktion 528 mal gemacht in verschiedenen Phasen der Stillungszeit. Gleich nach der Geburt war die Senkungsgeschwindig-

keit erhöht. Danach war sie während des ersten Monats schnell, später langsamer, gesunken, aber erreichte die normalen Werte erst nach vier Monaten.

Bei den Müttern von »Frühgeburten» ist die Blutsenkungsgeschwindigkeit während des zweiten, dritten und vierten Monats wahrscheinlich höher als bei den Normalgeborenen. Kein deutlicher Unterschied in der Blutsenkungsgeschwindigkeit wurde festgestellt bei Müttern, die ihre Kinder ausschliesslich stillten, und bei solchen Müttern, die ausserdem Zukost gaben.

Sumario

Se efectuo la eritrosedimentación en 168 madres sanas en lactancia, 528 veces, durante las distintas fases del período de lactancia. Inmediatamente después del parto se encontró considerablemente elevada. Luego decendio rapidamente durante el primer mes, luego mas lentamente, pero no alcanzo el limete superior normal antes de haber transcurrido 4 meses.

Durante el segundo, tercer y cuarto mes después del parto la eritrosedimentación de las madres con niños prematuros es probablemente mas alta que la de las madres con hijos nacidos a termino. Ninguna diferencia bien definida ha podido establecerse estre la eritrosedimentación de las madres que daban exclusivamente pecho a sus niños, y las madres que daban ademas a sus hijos una alimentación complementaria.

FROM THE CHILDREN'S CLINIC, HELSINKI.
CHIEF: PROF. ARVO YLPPÖ, M.D.

Incubator Treatment of Premature Infants

by

AIRA KETOMAA and C.-E. RÄIHÄ

The oxygen incubator, introduced by LICHTENSTEIN and MANNHEIMER in 1944, has been used in the Scandinavian countries since that date. In Finland it is manufactured by AGA. The construction of a domestic oxygen incubator became an urgent problem when a large number of them were required for the new Children's Clinic and other child welfare institutions in Finland. The incubator was manufactured by Oy Santasalo-Sohlberg AB in Helsinki. Meanwhile, incubators had been designed in the U.S.A., and there were several types on the market. Of these, Isolette, the new Chapple incubator based on the original principles established at the Children's Hospital of Philadelphia and manufactured by Air-Shields Inc., Hatboro, Pa., is nearest in principle to that developed in Finland.

Our incubator differs from the Lichtenstein—Mannheimer model on which it is based in the following respects.

1. Outdoor air is used.
2. The rates of flow of the oxygen and air are in no way dependent on one another but may be varied as desired.
3. The incubator is heated by means of a water mantle through which gases are conducted to the chamber.

Air taken from the room may contain airborne bacteria. The purity of the air led into the incubator is as high as possible if it is taken directly from the out-of-doors, particularly as there are several treatment units in the same room. Feeding of air into the incubator is centralized and a compressor (Fig. 2) provided of sufficient capacity to distribute compressed air into different

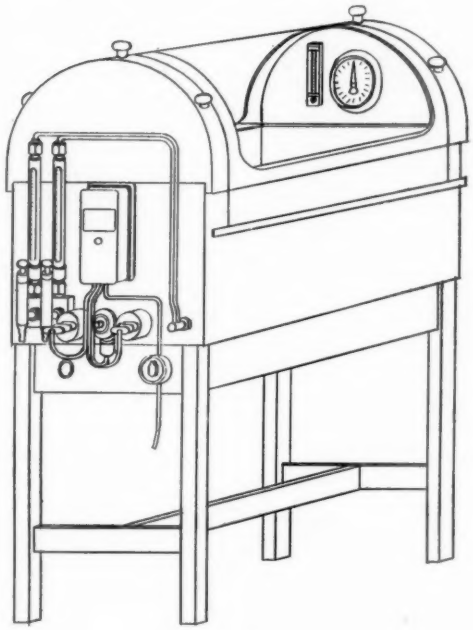

Fig. 1.

parts of the hospital. A two-cylinder pump (1) drives the air through an efficient oil and water separator cyclone (2) into a 300-liter container able to give 500 liters of air per minute at a pressure of 8 atm. The air then passes through oil and bacteria filters (4) into the room where the incubators are located. By means of a spray apparatus (5) and a humidity regulator (6) attached to it, the humidity inside the incubator can be adjusted as desired. Through reducing valves (7) the gases from the humidity apparatus are led to the incubators.

Humidity was adjusted at 50 %, the figure selected by DUNKLIN and PUCK in their investigations as that at which most of the airborne bacteria and viruses die within a very short space of time.

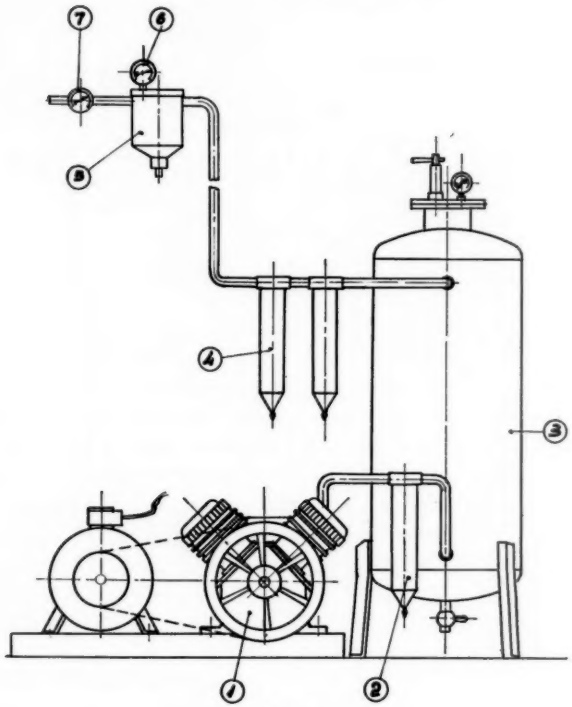

Fig. 2.

The stock of oxygen is also kept outside the therapy room. Four large oxygen bombs of 20 liters each are connected in series. Oxygen is administered to the incubators through reducing valves.

The incubator itself is a wooden case, $40 \times 68 \times 33$ cm in size, both ends of which are semicircular in shape. These ends support the roof of the incubator, which consists of a transparent celluloid sheet the lower edges of which are provided with narrow wooden strips to keep it straight and prevent curling. The incubator is opened by sliding the sheet along the edges of the incubator. To keep the incubator open, the ends are furnished with wooden pegs to which the wooden strip on the edge can be fastened

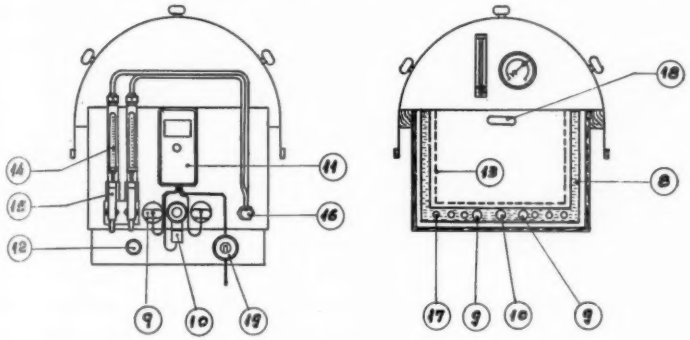

Fig. 3.

if necessary. The inner sides of the incubator are covered by a water mantle in a copper casing (Figs. 3, 8) which provides heat. The water mantle is heated by two heat elements (9). Its temperature and thus the temperature of the incubator may be accurately controlled by means of a heat regulator (10) with relays (11). 12 is a small signal lamp which lights up when the heating is on. Through 19 the current is transmitted to heat elements. Inside the water mantle, at about 1 cm's distance from it, there is a close-meshed net (13) on which the child's bed rests.

Separate rotameters (14) for oxygen and air are provided in the incubators and the gases are led to them through reducing valves (7). The rotameters are equipped with needle valves (15) by which the flow velocity of the gases is regulated. In this way the oxygen concentration of the air can be adjusted as desired, and as the volume of oxygen and air is great, it is easy to maintain a suitable carbon-dioxide percentage in the chamber. From the rotameter the gases, further mixed, are led through the water mantle several times via opening (16) and thin pipes (17) until they have attained the temperature of the water mantle and are thoroughly mixed. Gases are led into the chamber from one end at medium height (18). As the gas temperature is the same as that of the chamber air, the gases mix easily with the air and spread evenly all over the chamber. This continuous flow of gas

keeps the air in the incubator warm without any special lamp heaters even while the incubator is partly opened. The temperature decrease in half an hour with the lid ajar — roughly one third open — was only 1° C (from 33° C to 32° C while the room temperature was 25° C).

Inside the incubator there are a hygrometer and a thermometer. The installation of a scale which will allow the child to be weighed without being taken out of the incubator is also planned.

Summary

The authors describe an incubator for the treatment of premature infants in use at the Children's Hospital in Helsinki.

Résumé

L'auteur décrit une couveuse pour le traitement des enfants prématurés, en usage à l'hôpital pédiatrique d'Helsinki.

Zusammenfassung

Die Verfasser beschreiben eine Couveuse zur Behandlung von Frühgeburten, der im Kinder-Krankenhaus in Helsinki im Gebrauch ist.

Sumario

Los autores describen una incubadora para el tratamiento de los prematuros en el hospital de niños de Helsinki.

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Does Chorea Cause Carditis?

by

BERNHARD LANDTMAN

There are many theories about the true nature of chorea. At the present time, this disease is generally regarded as a major manifestation of rheumatism. However, there is still considerable difference of opinion about the importance of chorea as a cause of heart disease. Many authors dealing with this subject do not differentiate between these two conditions, chorea and rheumatic fever, with regard to their effect on the heart. It is well known that a large proportion of children with rheumatic fever show some signs of carditis more especially in their electrocardiograms; the figure of the incidence of this given by different authors varies between 40 and 100 % (COHN and SWIFT 1924, ASH 1936, DAVISON 1946, and others). A similarly high incidence of cardiac involvement is also said to be found in chorea (SCHWENTKER 1940, FEER 1941, HEFFER 1941, and others). Some authors, on the other hand, have observed that chorea, particularly when there is no evidence of other accepted rheumatic manifestations, is relatively seldom followed by heart disease (JONES and BLAND 1935, CLARKE 1940, FRIEDLÄNDER and MANNHEIMER 1944, and others).

In order to study this problem, detailed information has been gathered about eighteen children who in recent years have been treated for chorea at the Hospital for Sick Children, Great Ormond Street, and the Paediatric Department, University College Hospital, in London. Sixteen of the children were treated as inpatients, the length of their stay at the hospitals varying between three weeks and three and one half months (average one month three weeks).

Table 1

Clinical data about 18 children with chorea.

	Sex		Age in Years			Previous Rheumatic Infections	Duration of Chorea Before Admission (Weeks)			Signs of Rheumatic Infection	Fever	BSR (mm/1 hour)	
	Boys	Girls	4—8	9—12	13—16		1	1—2	3—4			Below 10	Above 10
No. of Cases	3	15	7	10	1	2	10	7	1	2	1	14	4

	Shape of the Heart in X-Ray		Murmurs			Pulse Rate (beats/min.)			Electrocardiogram	
	Normal	Abnormal	None	Systolic	Systolic and Diastolic	60—80	80—100	100—120	Normal	Abnormal
No. of Cases:										
Uncomplicated	16	—	13	3	—	6	10	—	16	—
Complicated	—	2	—	—	2	—	1	1	—	2

Fifteen of the children were girls and three boys. Seventeen of them were under twelve years of age at their first attendance. In none of the cases had there been previous attacks of chorea, and in only two was there a history of rheumatic infection affecting the joints, three and four years, respectively, before admission. In no case was the appearance of chorea said to have been preceded by a throat infection. The duration of the typical symptoms of chorea before admission to the hospital was on the average three weeks (one week to two months). On admission, two children, namely those with a previous history of rheumatic fever, revealed tenderness and swelling of the joints and subcutaneous nodules. One of these children had fever during the time of observation, while the rest had a normal temperature. The blood sedimentation rate (PAYNE's method) was raised only in these two cases of complicated chorea (25 and 45 mm in 1 hour, respectively). The remainder showed values below 15 mm in 1 hour (average 8 mm in 1 hour), which supports the observation that the sedimentation rate is often normal in cases of uncomplicated chorea (PAYNE and SCHLESINGER 1935, and others). Throat swabs, taken in fourteen children, grew in six instances haemolytic streptococci.

The Condition of the Heart. — In thirteen instances, auscultation of the heart showed no abnormality. A faint systolic murmur over the apex was noticed in three children throughout the whole time of observation. In the two cases of complicated chorea, on the other hand, a systolic and diastolic murmur was heard suggesting involvement of the mitral valve. In no instance was gallop rhythm heard.

On x-ray examination only the two children mentioned above showed cardiac enlargement, the rest of the children having a normal cardiac outline.

The heart rate was generally characterized by lability, but in only one child was a pulse rate of over 100 beats a minute observed continuously for longer than four days. The mean pulse rate of all the children was 85 beats a minute during the time of observation. The degree of sinus arrhythmia (RI) was estimated according to the formula introduced by SCHLOMKA and REINDELL

(1936). In normal children RI is about 11—15, but in cases of rheumatic carditis it is usually diminished (LANDTMAN 1947). In this investigation the mean value for RI was 13.4.

Examination of the electrocardiograms (standard leads), which in many instances were taken repeatedly, showed pathological changes only in the two complicated cases. One of these children had a partial heart block of W e n c k e b a c h type; the tracing of the other, aged seven years, showing a prolonged P-R interval of 0.20 second. In the cases of uncomplicated chorea the P-R interval varied between 0.14 and 0.17 second (average 0.14 second). The P waves, QRS complexes, ST segments, and the T waves in all eighteen cases showed no deviation from the values in normal children as described by SEHAM (1924), HAFKESBRING, DRAWE, and ASHMAN (1937), MANNHEIMER (1940), and others. The duration of systole (Q-T interval), which has been found to be prolonged in a large proportion of children with rheumatic carditis (DRAWE, HAFKESBRING, and ASHMAN 1937, and others), was estimated according to the formula introduced by HEGGLIN and HOLZMANN (1936). In all the cases of uncomplicated chorea the duration of systole was found to lie within the limits of the range of variation in normal subjects.

Discussion

None of the sixteen children with uncomplicated chorea in the first attack revealed obvious signs of cardiac involvement. However, the possibility must be borne in mind that the faint systolic murmur which was heard in three of these children was pathological in origin. On the other hand, FRIEDLÄNDER and MANNHEIMER (1944) have shown by means of calibrated phonocardiography that a systolic murmur due to active rheumatic carditis does not differ in amplitude or frequency from the murmur which can be found in a large proportion of normal children (on auscultation in 50 %, TAUSSIG 1940, and in about 80 % by means of phonocardiography, MANNHEIMER 1940). Moreover, in these three cases there was no fever and the sedimentation rate was normal, which is against the presence of associated rheumatic

carditis (WHITE 1947). Electrocardiography, a sensitive test of carditis, did not show pathological changes in the cases of uncomplicated chorea. On the other hand, those two children who in addition to chorea had other signs of a rheumatic infection showed clinical and electrocardiographic evidence of heart disease.

This raises the old question of whether all cases of chorea are rheumatic in origin. Standards for the diagnosis differ; at the two hospitals concerned the diagnosis from tic and habit spasm is made upon the form of the movements and the loss of power. However, it is clear that all writers do not use these criteria and therefore it is impossible to assess the incidence of this disease.

Evidence has been given that unlike all other rheumatic manifestations, chorea shows a diminishing incidence of carditis in each subsequent attack. It is possible that this phenomenon may be in part attributed to the inclusion of children with perverse movements other than chorea in figures quoted as rheumatic chorea, or that chorea has a multiple origin. It is also possible that the relatively frequent occurrence of a history of chorea in adults with acquired heart disease may be due to the fact that these patients are liable to rheumatic manifestations other than chorea which cause damage to the heart. The question remains whether all SYDENHAM'S chorea is rheumatic in origin and whether chorea alone and uncomplicated by other rheumatic manifestations causes carditis.

Thanks are due to Dr. B. SCHLESINGER and Dr. R. E. BONHAM-CARTER and the other members of the staff at the above-mentioned hospitals for allowing me the privilege of carrying out this investigation and to the British Council and the Academy of Finland for financial support.

Summary

A study of eighteen children with their first attack of chorea is presented. Only two of these showed evidence of carditis and both of them had had other rheumatic manifestations. The possibility of a multiple origin for chorea is discussed.

Résumé

On étudie 18 enfants ayant présenté une première attaque de chorée. Des signes de cardite ne furent mis en évidence dans que deux cas qui avaient montré l'un et l'autre d'autres manifestations rhumatismales. On discute possibilité d'une origine multiple de la chorée.

Zusammenfassung

Eine Untersuchung über Chorea bei 18 Kindern im ersten Anfall. Nur 2 von ihnen hatten Zeichen von Karditis; beide hatten ausserdem Zeichen von rheumatischer Infektion. Über die Möglichkeiten einer multiplen Ätiologie für Chorea wird diskutiert.

Sumario

Se estudian 18 niños con su primer ataque de corea. Solamente dos de ellos mostraron evidencia de carditis y ambos habian tenido otras manifestaciones reumaticas. Se discute la posibilidad de un origen multiple de la corea.

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FROM THE DUTCH CENTRAL INSTITUTE FOR BRAIN RESEARCH IN AMSTERDAM. DIRECTOR: PROFESSOR DR. B. BROUWER.

On serious intracranial Birth Injuries in spontaneous Delivery at full Term

by

CORNELIA DE LANGE

Part I

Hemorrhages in the pia-arachnoid and in cerebro and destructive processes in the brain are of frequent occurrence in the newborn. This is especially true of premature infants, but even if a normal end of the pregnancy is reached and no artificial help is necessary, there is no certainty that the child's brain is not impaired.

ASCHOFF is of the opinion that practically hemorrhages occur in every birth. Everything depends on their localization and extension and on whether or not they will disappear without leaving any remnants. In studying the literature we come to the conclusion that our constitutions and perhaps also our characters are as much subject to our birth as to our inherited chromosomes.

In their extensive and accurate investigations PH. SCHWARTZ and his co-workers (the school of Frankfurt o/M) observed that the majority of the hemorrhages in question were situated in the circulatory system of the vena magna Galeni. WOHLWILL stresses their frequent occurrence in the centers of germination round the ventricles. Cortical hemorrhages and those in the white matter are often associated. Rather frequently only hemorrhages in the white substance are observed, while uncomplicated cortical lesions are of rather rare occurrence.

In the course of one year, three cerebra could be investigated in the Central Institute for Brain Research, all of them of children born after spontaneous parturition at term. Twice only was the brain cortex primarily impaired, while in the third case there was a hemorrhage in the right posterior horn and also a diffuse brain process, which will be discussed later.

Case 1. Lu, second child of healthy parents, was born at term on August 20, 1945. Parturition was uneventful. Information about the first days of the child's life is not available. He was breastfed for a period of three months. During these months symptoms of illness were evidently lacking; at least nothing is mentioned in the anamnesis. After the age of three months the infant became obstipated and every few weeks there was an attack of fever. Sometimes a flux from the bowels occurred.

The child was admitted to hospital (*Zuiderziekenhuis* in *Rotterdam,* head of the Paediatric Department Dr. J. H. P. JONXIS) on March 23, 1946. Three days before that date he had become ill with fever and slight diarrhoea. The house physician prescribed »tablets» (probably a sulfa-preparation) and had weak tea substituted for the milk in the child's bottle. On the evening of March 22 the temperature registered 38° C.; during the day the child had cried continually, but that night he was very quiet and on the morning of March 23 the mother found him subconscious in his crib. Convulsions were not observed. The little patient had coughed frequently during the preceding days and now and then there had been a crowing sound on inspiration resembling that in tetany.

It must be mentioned that an elder brother of the child had died with symptoms resembling those which our patient presented during his stay in hospital, and that a child born after the death of *L* also presented cerebral symptoms. The feeding of our patient had been characterized by an adequate supply of vitamins.

Status of the Child on Admission to the Hospital. The patient gave the impression of being seriously ill, laying in a passive attitude with a temperature of 39.7 °. The pupils were narrow and without reaction to light, the alae nasi dilated actively, while over both lungs there was breathing of a rough character. Weight 6 510 grams. Age seven months. The knee jerks were present, R = L. The plantar reflexes could not be elicited.

Shortly after admission a convulsive fit occurred. Luminal was prescribed, but notwithstanding clonic spasms of both arms and legs persisted. The child was put into a permanent bath and his temperature fell gradually; at three in the afternoon it was 35.5°. The right arm was twitching intermittingly. The pupils were still narrow and without reaction to light. At six in the evening there were some fits of coughing. Respiration was slow and deep.

The blood sugar was estimated at 130 mg%. Next day (March 24) the condition was practically unchanged, but the fever had subsided. No pupillar response to light. On March 25 pauses in the respiration were occasionally noted. All extremities were now spastic. The pupils presented a slight reaction to light. BABINSKI's reflex was present, as were also the knee jerks on both sides. A blood transfusion was given and followed by a standstill in breathing. The transfusion was stopped. In

the evening blood was given intramuscularly and the child was also given oxygen. Next day there was occasionally irregular respiration. Spasms were again present, especially in the legs. Examination of the blood: Ca 10 mg%, anorganic phosphate 5.1 mg%, phosphatase 9 units. Leucocytes 11 800, differential formula: eos. 1. bandforms 2, segments 74, lymph. 22, mon. 1 %. Slight toxic granulations in the polynuclear leucocytes.

The general condition improved somewhat, but there was still a marked rigidity which reached its maximum in the morning. The child was staring; his eyes could not follow objects when presented. A second morphological examination of the blood yielded the following data: number of leucocytes 14 800, bandforms 6, segments 60, lymph. 31, mon. 3. Toxic granulations in the polynuclears.

Though not noted in the case history, the child's skin at this time evidently presented a yellowish hue as the HYMANS VAN DEN BERGH reaction proved directly a trace and indirectly a slight elevation.

On April 8 a lumbar punction was made. The NONNE and PANDY reactions proved negative, cells 13/3 (lymphocytes). The child was anaemic, the haemoglobin tax being 45 % and the number of erythrocytes 2 200 000.

On April 9 the neurologist, Dr. ZIEDSES DES PLANTES, was called in consultation. He suggested the possibility of a lesion of the brain stem. The rigidity continued. It seemed as if the child were now following light to some degree.

April 25. Urine examination revealed a positive albumen and a positive urobilin reaction; in the sediment a large number of leucocytes were found as well as many casts and sporadic erythrocytes. The yellowish hue of the skin was again striking. The child could not take the bottle (from the beginning of his stay in hospital gavage feeding proved necessary).

At the beginning of May the urine was again examined. Positive albumen and urobilin reaction. Leucocytes were still present but to a lesser degree. In the latter weeks the child had increased considerably in weight. Weight on admission 6 510 g, May 3. 6 720 g, May 14. 7 500 g. There were several attacks of fever during his stay in hospital.

The presence of albumen and leucocytes in the urine rendered an investigation of the renal function advisable. The blood urea was estimated at 0.43 g per l and the blood chlorine at 3.25 g per l. Values for the urine respectively 6.93 g and 1.87 g.

At the beginning of the second week of May there was again a rise in temperature. An X ray picture now revealed a triangular shadow on the right next to the heart (bronchopneumonia). When the child had again been afebrile for a week, he was discharged from hospital on May 17, 1946, in accordance with his parents' wish. There was still

considerable rigidity and the eyes were always closed. A tentative diagnosis of meningo-encephalitis e causa ignota was made. Gavage feeding still proved necessary (case history by the assistant physician, S. J. de Jongh).

The patient *Lu* was admitted to the hospital for the second time on September 22, 1946, and died on September 24. According to information the child, who was then thirteen months old, presented rigidity and spasms for some time after discharge. The rigidity lessened and the spasms disappeared as luminal was prescribed by the house physician. Evidently gavage was no longer necessary, as it is noted that the child took ordinary food, but in the weeks preceding his second admission to hospital feeding had become more difficult. On September 21 the breathing became difficult, the child grew dyspnoeic, and there was retention of urine.

Status on Admission. The patient was apathic, spastic, and had a greyish pallor. Feeding was possible only by gavage. The urine contained albumen, a large number of leucocytes, and also a considerable number of red corpuscles but less than the white. A lumbar punction yielded no particulars. There was hypothermia, irregular breathing, and the child's condition was rapidly becoming worse (case history by the assistant physician Dr. P. VAN DER ELST).

According to the anatomo-pathologist Dr. H. E. SCHORNAGEL of Rotterdam, the child had become blind and deaf at home but the case history does not mention this.

On postmortem Dr. SCHORNAGEL stated bronchopneumonia and pyelitis to be present. The child's brain was granted by him and the prosector Dr. M. STRAUB to the Central Institute for examination.

Weight of the brain 364 g; this is not more than the normal weight in a newborn child. According to RÖSSLE and ROULET (cited after BROCK[1]) the brain weight of boys at the age of one year is as much as 965 g and in girls as much as 944 g.

Macroscopical Examination. — There was a greyish discolouration over both hemispheres, also at the base (leptomeningitis chronica?). After the pia mater had been removed from the greater part of the brain, a slight yellow tinge was visible on the left parieto-occipital lobe, and there may also have been some yellow discolouration on the symmetrical part of the right side. The arteria basilaris and the vertebrales had a normal aspect.

A marked diffuse and almost symmetrical polygyria was present. This was not a real microgyria (which is a developmental error), for

[1] BROCK, J.: Biologische Daten für den Kinderarzt. Berlin. Julius Springer. 1932—1939.

the small ridges typical of the latter were lacking. The Sylvian and Rolandic fissures were traceable. The brain stem was separated from the rest by a cut through the pedunculi cerebri and the brain was further divided into vertico-frontal sections. There proved to be hydrocephalus of all the ventricles, the Sylvian duct being also dilated (hydrocephalus e vacuo). In several places in the brain cortex pori and ulegyria could be seen even with the naked eye. The corpus callosum was small and the centrum semi-ovale had diminished in size, but not considerably. The striatum, thalamus opticus, mid-brain, pons, and medulla oblongata showed nothing abnormal in their macroscopical aspect. Attention is drawn to the fact that the thalamus opticus was of normal size. The upper cervical cord also looked normal, the rest of the cord not being available for investigation.

Technique. Pieces of the following parts were taken and after embedding in paraffin stained with hematoxylin-eosin and with kresyl violet and toluidin blue: right and left cerebellar hemisphere, vermis, nucleus dentatus r and l, occipital lobe on the left with pia (the spot where the yellowish discolouration was seen), left motor cortex, left gyrus frontalis I and II, III, medial part of frontalis I on the right side with gyrus cinguli, r. calcarina, fourth ventricle with pons and dilated Sylvian duct. Furthermore: putamen and globus pallidus and thalamus opticus on the right side, the olivae inferiores and the upper part of the cervical cord. For the HOLZER stain (fibrillar glia) pieces of the right frontalis I, of the left lobus parieto-temporalis, and of the right centrum semi-ovale near the insula were taken. Frozen sections with Sudan III (fat stain) and hematoxylin were made of the right insula.

Microscopical Examination. There was no meningitis, but almost everywhere the pia arachnoid contained numerous cells, partly »Körnchenzellen», partly small round ones. The connective tissue had increased and there was a large number of widened, hyperemic blood vessels. A few calcified ganglion cells were found. The brain showed no signs anywhere of remnants of an encephalitis, nor were any congenital anomalies found.

The cortex cerebri presented great destruction, with formation of pori in different developmental stages. Generally the pori were limited to the cortex; seldom a porus was found in the cortical white substance. Different parts of the latter, however, contained a large number of transport cells (fat-containing cells). These cells showed very clearly in the frozen sections stained with Sudan III, but they were also readily detected in the sections stained with hematoxylin-eosin. They appeared as clear round spots, the nucleus usually lying in the periphery.

The pori were generally to be found on the border of the cortex and the cortical white substance but belonging to the former. Fig. 1. Some of them were situated in a more peripheric part of the cortex. In general,

Fig. 1. Pori in the cortex.

the first layer, the lamina zonalis, was present in several spots thickened by fibrous glial formation, then followed the pori, which had for the most part destroyed the following layers, and then came a fibrous demarcation with calcified cells on the boundary of the cortical white matter. These calcified cells were ganglion cells; they stained black with haematoxylin and showed a clear nucleus.

Of all the parts of the brain investigated the regio calcarina and the insula were in the best condition, though not intact. It seemed possible that in these the pathological process was mild and of recent date.

On examining the pori formation more closely, it was possible to distinguish several developmental stages. Attention was drawn first to the empty, hollow gyri of small dimensions; they formed the so-called »cock's comb» convolutions. Fig. 2. At a very short distance from these other forms of pori also were encountered. With PH. SCHWARTZ I am of opinion that the hollow gyri represent the process of destruction in its oldest form, but it is remarkable that amoeboid glia were to be seen in the lamina zonalis corticis that covered them, as the formation of amoeboid glia is considered to be a process of recent date. Fig. 3. Perhaps this may be explained by a more recent process having attacked parts

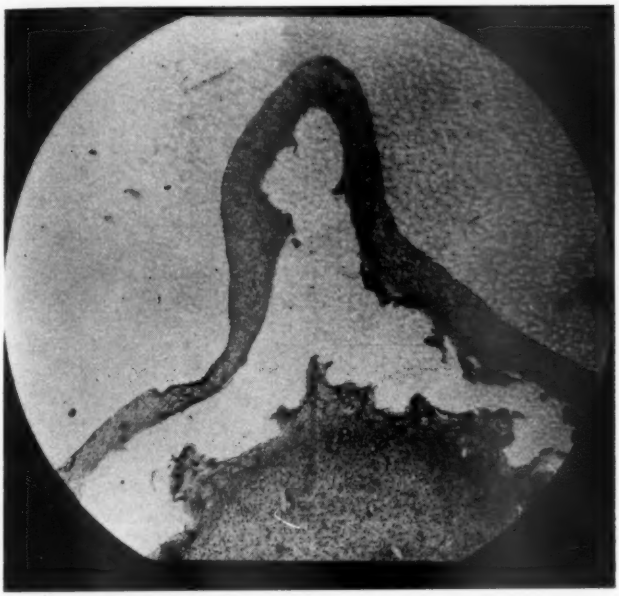

Fig. 2. Hollow (empty) gyrus.

that had already altered. This is in accordance with WOHLWILL's and SCHWARTZ's interpretations, which will be discussed later.

A second form was represented by pori which were still connected with the lamina zonalis by little bridges of glial tissue. These bridges were the remnants of the destroyed ganglionic layers.

Further processes of destruction were to be seen extending over a large part of a convolution and limited by a peripheric layer. In the destroyed area there was a network of fibers originating most probably from the connective tissue of the blood vessels. The vessels were numerous, the larger ones as well as the capillaries and precapillaries. It could be seen that from the vessel walls fibers repeatedly spread into the network. The latter contained »Körnchenzellen», calcified ganglion cells, and small threads of calcium probably lying in the walls of capillaries. Fig. 4.

Another developmental stage was represented by large and small empty, or almost empty, cavities. In some spots these pori were lined with a glial membrane and sometimes they contained a blood vessel and a shred of tissue.

Fig. 3. Amoeboid glia and calcified ganglion-cells.

Lastly, the pori which were formed more recently were still filled with fat cells. They were smaller than the cavities described above; sometimes several of them lay close together.

This is a general description of the condition of the cortex cerebri; we shall now give the picture of some gyri in detail.

The motor cortex showed a thickened pia-arachnoid with numerous hyperemic vessels; in some of them the wall of the vessel was partially calcified. Fig. 5. The upper layer contained many amoeboid glial cells, then came the pori of recent type with numerous fat cells. In these layers of the cortex calcified ganglion cells were seen and also amorphous deposits of calcium. Here all nerve cells had disappeared. On the border of the cortex and the cortical medulla the amoeboid glial cells were abundant. The white matter contained many fat-laden transport cells.

In the smallest gyri of the motor area the cortical medulla presented numerous amoeboid glial cells, many of them having lost their nucleus. The pia-arachnoid of the *calcarine* contained many hyperemic vessels and an increased number of cells. In the lamina zonalis there were, besides amoeboid glial cells, normal cells also. There was a minor formation of pori which must have been situated in the third cortical layer, as the three parts of the granularis interna were almost intact. The same is true of the layers 5 and 6 and the cortical medulla.

Fig. 4. a. Longitudinal destruction. b. Pia-arachnoid.

Fig. 5. Calcified vessel-wall in pia-arachnoid.

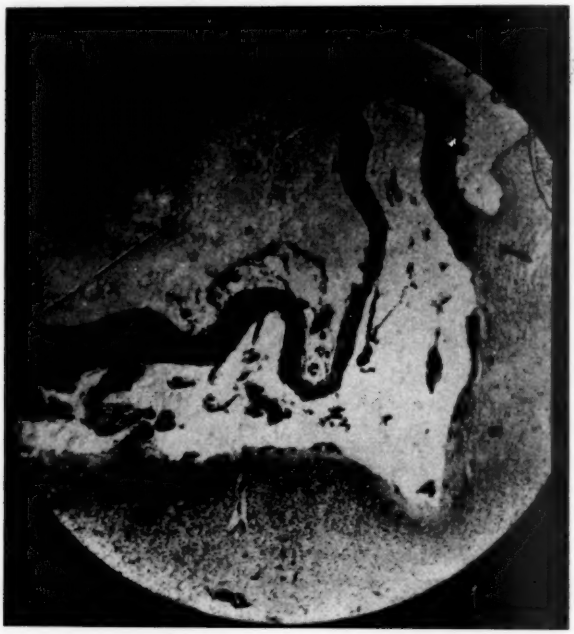

Fig. 6. Ulegyria with hollow gyri.

Gyri frontales II and III. Here were many cavities in the cortex which at some spots had led to the formation of hollow convolutions, some of which, however, contained some vessels and fibrous glia. Next to these the destruction process could be seen in recent stages.

Gyrus frontalis I: small hollow gyri, the lamina zonalis containing many amoeboid glial cells and in its interior border calcified cells. The small bridges described above could also be seen here.

Gyrus cinguli and adjoining part of gyrus frontalis II. The gyrus cinguli showed a serious process of destruction, mostly in a recent stage. In this part of frontalis II there were hollow convolutions with the aspect of cock's combs (ulegyria). Fig. 6.

Occipital cortex on the left (where the yellowish discolouration was visible). Here were large cortical cavities, the lamina zonalis containing calcified ganglion cells and also the part adjoining the cortical white matter. Of the nerve cells nothing was left. On the other side of the

same gyrus the process of porus formation could be seen as described sub 3. At the basis of this side of the occipital gyrus there were also calcified ganglion cells. The cortical medulla contained amoeboid glial cells in great number. In the pia arachnoid numerous hyperemic vessels and round cells were seen and some »Körnchenzellen».

Insular cortex. Here the process was of recent date and very moderate in degree.

Slides stained according to HOLZER's method showed an increase in the fibrous glia in different parts of the cortex, but not to an excessive degree. Those parts of the brain which appeared normal on macroscopic investigation (cerebellum, striatum, thalamus, midbrain and upper part of the cervical cord) proved to be without primary lesions on microscopical examination. As the retrograde processes have been thoroughly examined in Case 2, they were not studied here.

The results of the investigation in the child *L.* (Case 1) are on the whole in accordance with the findings of SCHWARTZ in cortical lesions; this holds good especially as regards the occurrence of small hollow gyri. Remnants of hemorrhages were not observed, but in one of the frontal gyri a small recent hemorrhage was seen.

It is probable (one may take it as almost certain), that once the vascular neuro-apparatus has been impaired, it becomes abnormally irritable (RICKER).[1] This exaggerated irritability, either by itself or influenced by the unrestrained action of stimuli, leads to an abnormal width of the vessels and a lessened velocity of the bloodstream (stasis, praestasis, haemorrhages per diapedesin). In the originally damaged portions of the brain SCHWARTZ[2] could observe more recent processes as well as older ones. The latter he terms »akute Spätfolgen». In the same way WOHLWILL explains that next to the original focus destructive processes occur which may spread over a large part of the brain. In the literature on the subject of the brain injuries, the presence of fat cells in the damaged parts even years after the birth injury is sometimes mentioned. We might venture to suggest that they belong to a recent process in an old focus.

[1] RICKER, G.: Virchow's Arch. f. path. Anat., *226*, 180, 1919.

[2] SCHWARTZ, PH.: Ergebnisse der inneren Med. u. Kinderhk. *31*, 165, 1927.

The examination of the brain of our patient proves the correctness of the above-cited opinions. A diffuse traumatic polygyria was found and a developmental arrest in the growth of the brain.

Epicrisis. Now that we are in possession of the facts concerning Case 1, it is interesting to review the whole course of the child's illness. A birth injury, a subdural hemorrhage, led to a traumatic polygyria and underdevelopment of the brain with severe destruction of the cortex cerebri, leaving the cerebellum and the basic portions of the brain intact. The subdural hemorrhage took place in the parieto-occipital parts of the brain and exercised a pressure on the cortex, but in WOHLWILL's opinion the lesions did not halt there. The vascular neuro-apparatus, having once been impaired, was no longer capable of resisting the normal or abnormal stimuli of post-uterine life and responded with praestasis and stasis which in their turn produced new lesions. In favour of WOHLWILL's opinion are the facts that though the child was already thirteen months old, amoeboid glia (die zerfallende, isolierte Gliazelle von SCHWARTZ) and »Körnchenzellen» were still abundant in some parts of the brain, for instance the insular region. Also, in these portions the pori were still in statu nascendi, being filled with cells with lipoid destruction products.

It must be kept in mind that the parturition was quite normal. Many doctors are still unacquainted with the fact that a normal delivery may give rise to a serious birth injury. Furthermore, it is of interest that the birth injury did not show any symptoms before the child attained the age of seven months. Unfortunately we have no information about the first days of life. It is very improbable, however, that rigidity, spasms, and convulsions as described above would entirely have escaped the mother's notice. In fact, it is well known that even malformations of the brain may produce symptoms only after latent periods of different duration. In the light of WOHLWILL's hypothesis mentioned above, it seems probable that in our case extra-uterine circumstances spread the lesions over a large portion of the brain, and that symptoms showed themselves only when a certain point was reached.

The correct diagnosis of a status cerebralis in an infant is mostly extremely difficult and very often wrong regardless of the competence of the neurologist. Thus in our Case 1 a tentative diagnosis of lesion of the brain stem had been made, whereas the brain stem proved to be intact and the cortex severely injured. Very often, too, the diagnosis of meningo-encephalitis is made, but encephalitis in infancy is of relatively rare occurrence.

As for the extra demands on the cerebrum of our patient which could give rise to a spread of the pathological process, there were the attacks of fever from which the child suffered from the age of three months. Very probably they were caused by a pyelitis observed during life and found at the post-mortem. Such attacks are often typical of pyuria in infants. If not treated these may persist over a long period even in cases where no congenital anomaly of the tractus uropoeticus is found. Once a fever attack was accounted for by bronchopneumonia and the immediate cause of death was probably also bronchopneumonia in a child in very bad condition, the pyelitis persisting all the same. The yellowish skin colour in pyuria of long standing is well known and is generally caused by urobilin passage into the blood and urine, as a sign of an impaired function of the liver (LASCH, FISCHER, SILBER[1], FINKELSTEIN[2]). On rare occasions there may also be bilirubinuria without definite diagnosis of the case as sepsis. In the beginning of the patient's stay in hospital the crowing sound on inspiration suggested the possibility of the convulsions being a symptom of tetany, but the chemistry of the blood ruled this out.

Case 2. Child B. Professor B. BROUWER and I myself made an examination of an intracranial birth injury in which the primary lesions were limited to the cortex, but unlike Case 1, some parts of the cortex proved entirely intact. This circumstance provided an occasion to study the projection of the brain cortex on the thalamus opticus (for particulars respecting this projection and some other interesting facts see the Proceedings of the Royal Dutch Academy of Sciences. Vol. LI No 8, 1948).

This child died at the age of six months. During the first days of

[1] LASCH, FISCHER, and SILBER: Monatschr. f. Kinderhk., 46, 1931.

[2] FINKELSTEIN, H.: Säuglingskrankheiten. 4. Auflage.

Fig. 7. Structure resembling a cactus.

life she was cyanotic with irregular breathing accompanied by convulsions. The latter ceased after a few days, and the child was sent home, apparently cured, but two months later the convulsions returned with increasing intensity. The patient was re-admitted to the hospital, an operation was performed on the skull, and she succumbed a few hours later.

The brain weight was only 345 g and there was an arrest of growth in the skull and in the brain with ulegyria and polyguria. The microcephaly was to be seen, as a result of the lack of formative stimulus from the brain growth on the growth of the skull. In this case also an extensive formation of pori was found in the cortex, but a very striking microscopical feature was the presence of small, apparently cut off pieces of round or oblong form lying mostly in the pia-arachnoid but partly in the cortex. In several spots the pieces in the pia-arachnoid formed together a structure resembling a cactus plant. Fig. 7. The pieces were surrounded by a thin layer of connective tissue originating from the blood vessels. We did not find this process mentioned in the literature.

There were still other microscopical differences between this case and that of the child *Lu*. In Case 2 we found only amorphous

deposits of calcium (or pseudocalcium) and no calcified ganglion cells, the fibrous glia and the astrozytes were more abundant, and the tissue bridges described in the child *Lu* were lacking.

Case 3. On the day following birth the child *v.R.* was taken into hospital with her mother because the latter was suffering from total rupture of the perineum. This was curious, as parturition occurred at term, but the child weighed only 2 050 g. During the pregnancy and earlier the mother was in good health.

The child had convulsions from the beginning. On admission the pediatrician J. K. HUYSINGA stated a backward position of the head and a crossing of the legs. The cranium seemed small and the child gave the impression of debilitas. The day after admission the right big toe became gangrenous and bullae appeared. Gangrene and bullae spread over the other toes and then over the lower legs; the same was true of the arms. The impression was given that the extremities were slowly dying. Livores appeared. Convulsions persisted. The temperature ran an irregular course.

On the third day of life a lumbar punction was performed. Evidently the quantity of fluid removed was small, as it was not sufficient for NONNE's reaction. The PANDY reaction proved positive, but only feeble. The total albumen content was estimated at 0.43 ‰; the fractions could not be determined. The formol-goldsol-reaction of LANGE, the benzoë-sol reaction of GUILLAIN and the mastix sol reaction of EMANUEL-KAFKA by the pathologist were regarded as slightly pathological in a child. We did not succeed in finding the normal values for these reactions in the newborn. The number of cells in the liquor was 52/3; their nature is not stated. The number of red cells was 15/3.

On the tenth day post partum an investigation of the blood was made; RBC 4 790 000; WBC 22 700, hgl. 94 %, colour index 0.98. Rodforms 22, segments 42, eosinophils 3, lymphocytes 18, monocytes 15 %. Toxic granulations of moderate intensity. The child was unconscious most of the time and did not take her food. Death occurred on the thirteenth day of life.

Clinical diagnosis: congenital meningitis.

Post mortem (Dr. R. R. ROCHAT). Length of the cadaver 51 cm, wt. 2 050 g. Desiccated bullae on the right hallux and the toes of the right foot. The top of the big toe was gangrenous. The anterior fontanel measured $2\frac{1}{2} \times 2$ cm; the larger part was already ossified. Falx and tentorium proved intact; the same was true of the surface of the brain and the cerebellum. The basis cranii was also normal. No hemorrhages were seen. On cutting the brain the pathologist mentioned widespread pinpoint haemorrhages, especially in the central parts. On examining the brain at the Central Institute for Brain Research we

could not find any macroscopically visible haemorrhages. It seems probable therefore that widened hyperaemic vessels were seen at autopsy.

The brain was presented to the Central Institute for Brain Research, but it was not complete, the cerebellum being lacking, as also the left thalamus opticus, the regio subthalamica, the pons, medulla oblongata, and the upper part of the cervical cord. The post mortem yielded few further particulars, the visceral organs being normal and especially the spleen of normal size and appearance. In the pericardium a teaspoon of slightly haemorrhagic fluid was found. The heart was of normal size, the left ventricle being empty and the atrium containing a small quantity of dark blood. On the anterior wall of the right ventricle and also on the left ventricle yellow spots the size of a pinpoint were seen; these were surrounded by a red halo. These spots were not examined microscopically by the pathologist. He stated: »foci of inflammation?» That may have been, but the possibility that they were vascular processes, as will be described later on, cannot be ruled out.

Macroscopic Examination. On the surface of the brain no anomalies were seen. There was no hydrocephalus. A slight dilatatio cavi septi pellucidi was present. In the right posterior horn a blood clot the size of a peanut was found. There was no meningitis.

Technique. Parts were cut out and embedded in paraffin and the coupes stained after NISSL and with hematoxylin-eosin from: the left occipital pole, right gyrus occipitalis primus, medial part of the pallium with neighbouring centrum semi-ovale Vieussenii on the left side, right thalamus opticus, gyrus frontalis primus, striatum right and left, lobus temporalis, posterior part, on the left, lobus temporalis, anterior part, on the right; area round the third ventricle on the left, posterior horn of right ventricle with blood clot. Frozen sections of the occipital pole and middle of the pallium were stained for fat with Sudan III and haematoxylin.

Microscopical Examination. There was no meningitis. The pia-arachnoid contained a considerable number of mononuclear cells. No polynuclear leucocytes were found nor cuffs round the vessels. At some spots small hemorrhages were visible.

In the *posterior horn of the right ventricle* the clot had somewhat retracted. Fig. 8. It contained pigment and some traces of organization. Apparently the plexus chorioideus had been somewhat compressed, but otherwise it looked normal, as did the ependyma. Round the ventricle small hemorrhages were visible, as were vessels with stasis and further conglomerations of leucocytes in the middle of vessels surrounded by a halo of red blood corpuscles lying partially in the wall of the vessel, partly outside it. Fig. 9. Vere rarely large cells (macrophages ?) were seen bordering the vessels in some places with the leucocytes in their midst. Scarce and small conglomerations of glial cells were seen throughout the tissue round the ventricle, as also calcified ganglion cells and amoe-

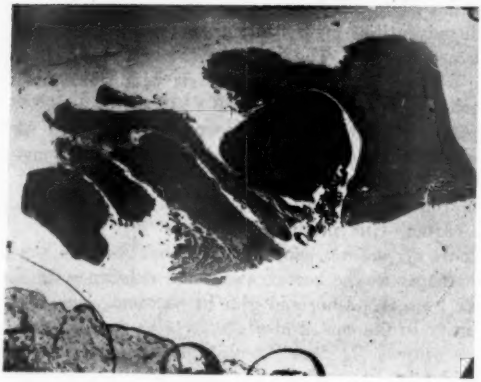

Fig. 8. Blood clot in the right posterior horn.

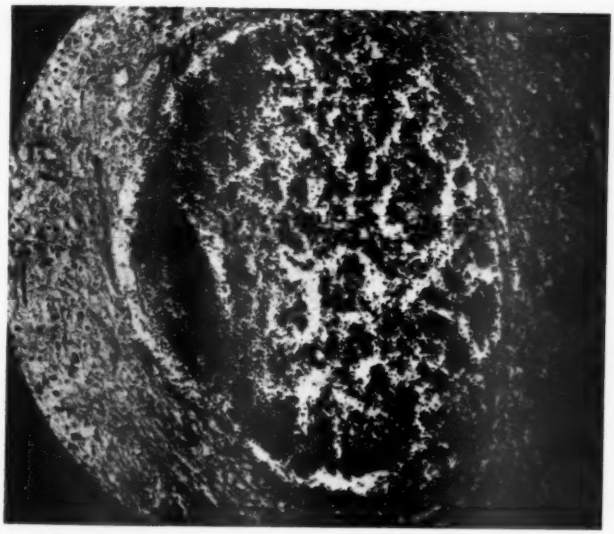

Fig. 9. Stasis in vena, leucocytes in the middle, erythrocytes peripherally.

boid glia in the white substance. A small vena cut longitudinally presented a thin adventitial layer of lymphocytes or glial cells.

R. gyrus occipitalis I. The layers of the cortex were practically normal, but the white substance showed vessels with white stasis and round them amoeboid glia.

R. occipital pole. Here were numerous vessels with white stasis in the cortex and the white substance, but also parts with normal appearance. Amoeboid glia in the white substance.

L. gyrus frontalis I. Small haemorrhages in the white substance, also some in the cortex. Glia normal.

Middle part of pallium with centrum semi-ovale on the left. Stasis, small haemorrhages in the cortex and white substance, in some of them some calcium present. Amoeboid glia in centrum semi-ovale Vieussenii, a small quantity in the cortex also.

Thalamus opticus R. Small recent hemorrhages, white stasis, very little amoeboid glia.

Striatum R. Small hemorrhages, white stasis with red border, the erythrocytes lying for the most part outside the vessel walls (diapedesis), partly in the walls. There was also diapedesis in vessels not showing the conglomerations of white cells in their midst. No amoeboid glial cells present. Centers of germination beneath the ependyma. In some spots vessels surrounded by a red halo could be seen with the naked eye.

The left striatum presented the same picture.

Lobus temporalis. Widened, hyperemic vessels, but no other circulatory disturbances. Amoeboid glia absent. The same was true of the *lobus temporalis 1 in its posterior part.*

Region round the third ventricle on the left. Small hemorrhages; vessels with white stasis and red bordering.

Occipital pole stained for fat. There were numerous fat cells, principally in the white substance; the cortex and the pia-arachnoid showed only a few of them.

Middle of the pallium. Here the fat cells were less numerous.

Epicrisis. The clot in the posterior horn of the right ventricle explained the convulsions the child suffered from. In infancy convulsions may be elicited from every impaired part of the brain. Probably the reactions of LANGE, GUILLAIN, and EMANUEL KAFKA may be regarded as normal in a newborn child, as there was no meningitis.

As far as examination was possible, widened and hyperemic vessels, mostly small venae, were found all over this brain. This vascular widening must have caused a decreased velocity of the

blood stream, a red stasis. In the greater number of vessels the red corpuscles were seen thronged together; they could no longer be distinguished separately. Moreover, small haemorrhages were found, the vessels belonging to which generally could not be found; the same was also true in hemorrhages of somewhat larger size. Widened vessels were seen presenting in their midst a mass of leucocytes; the red corpuscles lay partially in the vessel wall, but for the most part grouped in a halo outside the walls (diapedesis). Sometimes, but not often, the leucocytes left the lumen of the vessel and the erythrocytes remained in it. Now and then a small vena was seen longitudinally cut and containing only white bloodcells.

The vessels with leucocytes in the middle and the red halo were very similar to the pathological findings in the heart; unfortunately the latter were not examined microscopically by the pathologist. As some of those in the brain could be seen with the naked eye, a certain doubt arises as to his interpretation of them as inflammatory foci. Granted that these circulatory symptoms with the changes in the distribution of the blood elements showed a resemblance to miliary abscesses, in studying the different grades of stasis the conviction grows that this diagnosis is wrong. Repeatedly in the white center of the above described vessels amorphous deposits of calcium or pseudocalcium could be distinguished. With a high magnification bacteria in those parts could not be found. In brains damaged by birth calcium may be found very early. SCHWARTZ, in one of his cases, mentions the sixteenth day of life, and in our Case 3 calcified ganglion cells were also undoubtedly present, i.e. on the thirteenth day after birth.

RICKER[1] describes histological pictures resembling miliary abscesses in brains after a commotio. At first he found an exudation of albuminous fluid from the vessels; these were lacking in our Case 3 but otherwise my findings are in accordance with those of RICKER.[1]

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[1] RICKER, G.: Die Entstehung der pathologisch-anatomischen Befunde nach Hirnerschütterung in Abhängigkeit vom Gefässnervensystem des Gehirns. Virchow's Arch. f. path. Anat., *226*, 180, 1919.

Is one justified in declaring the vascular changes and the degeneration of the astrocytes to amoeboid glia to be a result of an injury at birth? As regards the hemorrhage in the posterior horn of the right ventricle and the small hemorrhages spread in the brain, this is very probable, almost certain. We have to bear in mind however, that the child had led a vita minima (livores intra vitam), and we cannot preclude the possibility that during life the blood-circulation in the brain was already impaired and brought about a degeneration of astrocytes.

Summary

The author stresses the point that a normal delivery at full term in no way precludes serious intracranial birth injuries. Three observations are given with detailed microscopical investigation. The second case was studied by Prof. B. Brouwer and the author.

1. Serious cortical lesions with formation of pori and hollow gyri.

2. Traumatic microcephaly with localized (pseudo) microgyria and severe damages to the cortex. The cortical projection on the thalamus opticus was studied.

3. Large clot in the posterior horn of the right ventricle, small hemorrhages, and amoeboid glial cells over a large part of the brain.

Résumé

L'auteur souligne le fait qu'un accouchement normal à terme n'empêche en aucune façon la survenance de graves lésions intracraniennes. Trois observations sont présentées avec recherches microscopiques. Le second cas a été étudié par le Pr. B. Brouwer et l'auteur.

1. Des lésions graves corticales avec formation de pori et de circonvolutions excavées.

2. Microcéphalie traumatique avec pseudomicrogyrie localisée et lésions graves de la substance corticale. La projection corticale sur le thalamus optique a été étudiée.

3. Gros caillot dans la corne postérieure du ventricule droit. Petites hémorrhagies et cellules amiboïdes gliales se trouvant dans une grande partie du cerveau.

Zusammenfassung

Die Verfasserin betont besonders den Umstand, dass eine normale rechtzeitige Entbindung keineswegs ernste intrakraniale Verletzungen bei der Geburt ausschliesst. Drei Beobachtungen werden mit detaillierter mikroskopischer Untersuchung angeführt. Der zweite Fall wurde von Prof. B. Brouwer gemeinsam mit der Verfasserin studiert.

1. Ernste Verletzungen der Hirnrinde mit Bildung von Pori und hohlen Gyri.

2. Traumatische Mikrocephalie mit lokalisierter (Pseudo-) Mikrogyrie und schwerer Beschädigungen der Hirnrinde. Die Kortexprojektion auf den Sehhügel (thalamus opticus) wird studiert.

3. Grosses Hämatom im Hinterhorn des rechten Ventrikels. Kleinere Blutungen und amöboide Gliazellen in einem grossen Teil des Hirnes.

Sumario

La autora puntualiza que un parto normal a termino de ninguna manera excluye lesiones intracraneanas al nacer el feto. Se exponen tres observaciones con exámenes microscopicos detallados. El segundo caso ha sido estudiado por el Prof. B. Brouwer y el autor.

1) Lesiones corticales serias con formación de halogyria y porigyria.

2) Microcefalia traumatica con (pseudo) microgyria localizada y lesiones severas de la corteza. Se estudia la proyección cortical sobre el talamo optico.

3) Gran coagulo en el cuerno posterior del ventrículo derecho, pequeñas hemorragias, y celulas gliales amiboidales sobre áreas del cerebro.

FROM THE PHYSIOLOGICAL DEPARTMENT OF KAROLINSKA INSTITUTET (CHIEF: PROFESSOR C. G. BERNHARD) AND THE PAEDIATRIC CLINIC OF KAROLINSKA INSTITUTET AT KRONPRINSESSAN LOVISA'S CHILDREN'S HOSPITAL (CHIEF: PROFESSOR A. LICHTENSTEIN)

A Study of the Changes in the Alpha Frequency of Human Brain Potentials in Normal and Pathological Conditions

by

L. E. LARSSON, K. A. MELIN, G. ÖHRBERG, and KJ. ÖHRBERG

Introduction

Ever since the clinical application of the electroencephalographic method (EEG) the alterations in the alpha frequency which occur with advancing age have aroused considerable interest. As early as 1932 BERGER pointed out that the alpha frequency is low in children, and since then several authors who have examined children of various ages have been able to show that it increases with age (LINDSLEY 1936, 1938, 1939: SMITH 1937 and 1941: BERNHARD and SKOGLUND 1939 a). According to GIBBS and GIBBS (1944) definite decreases are to be met with in old age.

The above investigations for the most part were carried out on groups of subjects in which each individual was examined only once. HENRY is the only author who has followed up a relatively large number of subjects over longer periods. In his paper of 1944 he reported a series of investigations which covered a period of five to eight years. He found that the increase in the alpha frequency was uneven in its continuity. Less extensive investigations of a similar type have been carried out by SMITH (1941) and by ENGEL, ROMANO, and FERRIS (1947).

The subjects investigated by BERNHARD and SKOGLUND (1939) have been placed at our disposal and after a lapse of ten years we have reinvestigated their alpha frequencies together with those of an additional number of pathological cases.

Normal Cases

The material available consisted of sixty persons resident in Stockholm, and their examination was carried out in the electroencephalographic laboratory of Kronprinsessan Lovisas Children's Hospital. We used a Grass electroencephalograph, Model III. Silver disc electrodes were attached to the scalp with collodion. Between the electrodes and the scalp a thin layer of electrode jelly was introduced. The electrodes were placed symmetrically on the occiput and the »indifferent» electrode was placed on the right ear. The subject to be examined was placed lying down with closed eyes in an electrically shielded and almost dark room. All the examinations were made during the afternoon and evening after the subject had rested for at least half an hour. In the majority of cases the alpha frequency was determined by counting fifteen to twenty-five sequences, each of which lasted at least one second. Nine cases were excluded for technical or clinical reasons. As stated above, the previous records had been placed at our disposal for the purpose of comparison.

In all the records the alpha frequency was determined from both the right and the left occipital regions. No pronounced differences between the two were found.

All the normal cases showed an increase in the alpha frequency as compared with the findings ten years previously. In all but three cases such differences lay within the normal range of variation.

The diagrams in Fig. 1 indicate that the increase of the alpha frequency in the individual cases does not follow a curve that can be expressed by the formula of WEINBACH (1936), unless individual coefficients are used. On the contrary, there are marked individual variations. As pointed out by HENRY, these may be partly due to variations in basal conditions present when the examinations were made, such as different metabolic conditions (LINDSLEY and RUBINSTEIN 1937), or to the fact that the frequency was determined after varying length of the rest period (LOOMIS, HARVEY, and HOBART 1936, quoted by HENRY).

Table showing the alpha frequency in fifty-one normal subjects 1938 and 1948

No.	Sex	Age in Years 1938	Alpha 1938	Alpha 1948	Difference
80	♂	3/12	3—4	9.0	5—6
70	♂♂	11/12	6.6	10.1	3.5
195	♂♂	1	5.4	9.0	3.6
56	♀♂	1 11/12	6.8	8.9	2.1
34	♂♀	2 6/12	6.9	9.7	2.8
63	♀♂	3	7.2	9.4	2.2
58	♂♂	3	7.0	10.1	3.1
59	♂♂	3	6.7	10.1	3.4
134	♂♀	4	8.5	9.5	1.0
75	♀♀	5	8.4	9.2	0.8
20	♀♀	5	8.3	10.9	2.6
020	♀♂	5	8.4	9.7	1.3
174	♂♂	6	8.9	11.8	2.9
55	♂♂	6	8.2	10.0	1.8
15	♂♂	6	9.2	10.1	0.9
23	♀♀	6	7.7	9.9	2.2
8	♀♀	6	8.2	9.4	1.2
91	♂♂	7	8.0	9.2	1.2
031	♂♂	7	10.3	10.9	0.6
47	♂♂	7	8.6	10.8	2.2
12	♂♂	7	8.5	9.8	1.3
184	♂♀	7	7.5	9.2	1.7
29	♂♂	7	7.9	11.4	3.5
135	♂♂	7	8.7	9.3	0.6
179	♂♀	7	8.8	10.3	1.5
178	♂♂	7	7.5	9.4	1.9
164	♂♂	7	7.7	9.4	1.7
2	♂♂	7	8.0	10.8	2.8
169	♂♂	8	9.0	9.1	0.1
135	♂♂	8	8.7	9.3	0.6
034	♀♂	8	8.0	9.3	1.3
43	♂♂	8	8.9	11.2	2.3
151	♀♂	8	8.0	9.7	1.7
166	♂♂	9	9.0	10.5	1.5
56	♂♂	9	9.2	9.9	0.7
157	♀♂	9	8.3	11.5	3.2
185	♂♀	9	8.5	10.2	1.7
158	♂♀	11	8.4	8.6	0.2
24	♂♀	11	9.3	10.5	1.2
93	♀♂	11	8.4	10.3	1.9
021	♂♂	12	8.6	9.4	0.8
175	♂♂	12	9.0	10.9	1.9
120	♀♂	12	10.0	10.5	0.5
64	♂♀	13	9.5	11.3	1.8
132	♀♀	13	8.5	10.9	2.4
032	♀♀	13	9.2	10.4	1.2
138	♀♀	13	11.0	12.5	1.5
65	♀♀	13	8.5	10.1	1.6
21	♀♀	14	9.5	10.6	1.1
A	♂	28	10.7	11.1	0.4
027	♂	28	9.0	9.3	0.3

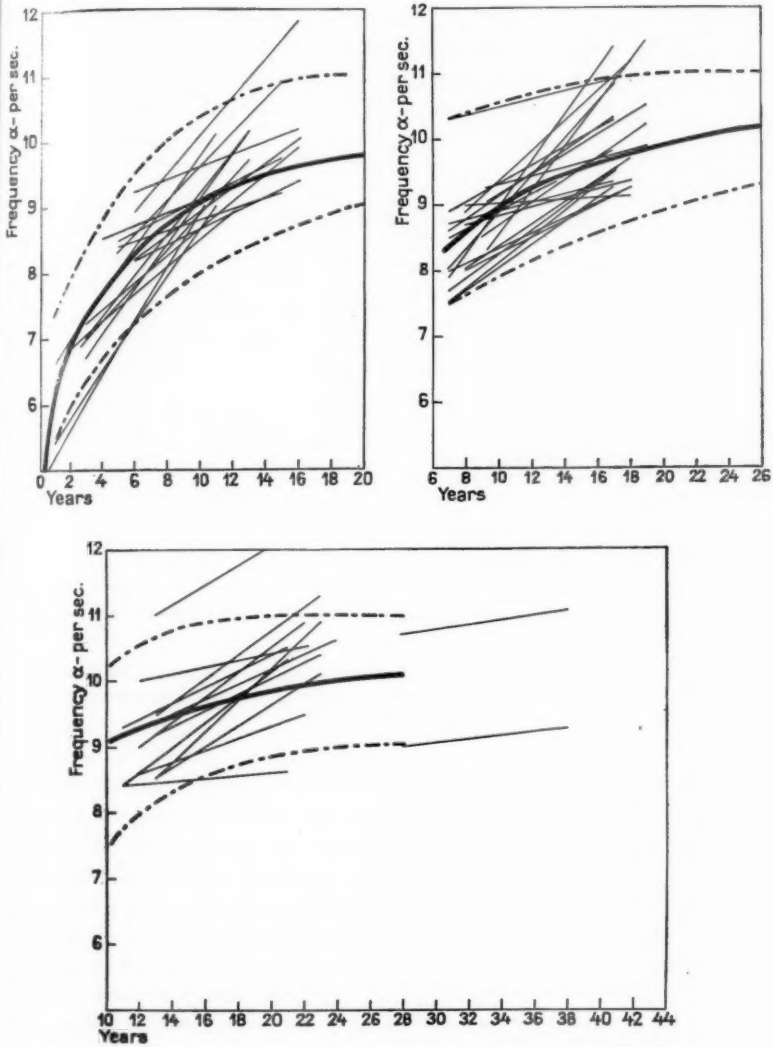

Fig. 1. Diagrams showing the alpha frequency in 1938 and 1948 in fifty-one normal cases. The thick solid line represents average values and the dotted lines range values according to BERNHARD and SKOGLUND (1939 a).

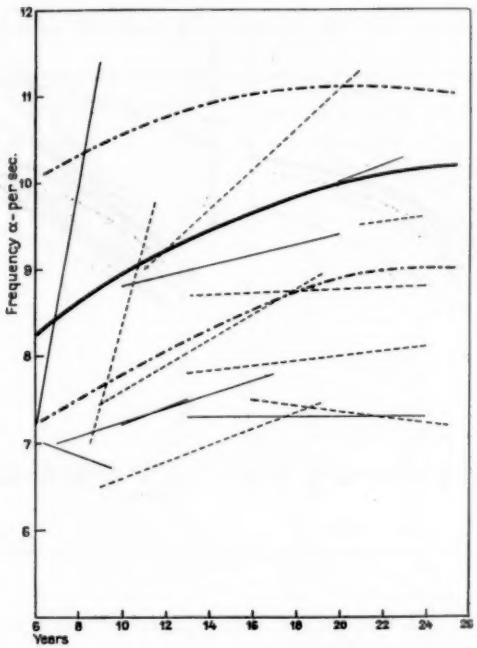

Fig. 2. Diagram showing the alpha frequency in 1938, 1945 and 1948 in fifteen pathological cases (solid lines, mongols; broken lines spastics and other mental deficients).

These variations may also be duo to head injury or infections (parotitis, etc.) having occurred during the intervening ten years. Among the cases reported by us there is scarcely one who had the complete history of a »normal subject». Indeed it is almost impossible to obtain a series of absolutely »normal» subjects.

The cause of the increase in frequency is a problem of considerable interest. When endeavouring to formulate a working hypothesis, we considered that due attention should be paid to the fact that every increase in frequency may take place in different ways. The increase may be continuous or discontinuous. When these possibilities are taken into account, allowance should be

made for the influence of different stimuli on the brain rhythms, the relative dysrhythmia of the EEG in children, and the imperfect development of interneuronal connections in the child's cortex. EEG examinations combined with cytoarchitectonic examinations are needed.

Pathological Cases

KREEZER (1939) examined a number of mongols but found no relation between alpha frequency and mental age in the mongolian type of mental deficiency. BERNHARD and SKOGLUND (1939 b) also examined a number of mongols, spastics, and mental deficients, and GUNNARSON (1945) continued their investigations on mongols and spastics.

In some of the above pathological cases they found a lower frequency than in normal cases and GUNNARSON's results indicate that the alpha frequency of mongols is usually below normal.

We have been able to carry out follow-up examinations on most of their cases and these were conducted under exactly the same experimental conditions as those on normal subjects.

Of the twenty-one patients examined, five were found to be too dysrhythmical to permit of a reliable analysis. In adidtion, one more is not included in the diagram; she was fifty years old and this might well have accounted for her lowered frequency.

The remaining cases are depicted in the diagram (Fig. 2). The frequency of four mongols was found on both occasions to be below the normal lower limit; two of these either showed no increase at all or a decrease in the alpha frequency since the preceding examination. In one case an abnormally large increase was evident. The remaining two mongols lay within normal limits. As regards the remaining pathological cases, four were below the normal lower limit. Of these four one showed a decrease in the alpha frequency and two were found to have an increase which was less than that of normal cases.

It would be interesting to correlate the EEG with histological findings in the cerebral cortex in pathological cases of the above types.

Table showing the alpha frequency in 16 pathological subjects.

No.	Age at 1st examin.	Mental age at 1st examin.	Alpha frequ. at 1st examin.	Age at 2nd examin.	Mental age at 2nd examin.	Alpha frequ. at 2nd examin.	Alpha-increase
			Mongols				
		1938			1948		in 10 years
111	7	—	7.0	17	—	7.8	+0.8
99	10	—	8.8	20	—	9.4	+0.6
94	13	—	7.3	23	—	7.3	±0
		1945			1948		in 3 years
I	5	<2	6.5	8	$2\,^{3}/_{12}$	11.4	+4.9
II	6	<2	7.0	9	$2\,^{2}/_{12}$	6.7	—0.3
III	10	$2\,^{10}/_{12}$	7.2	13	$3\,^{1}/_{12}$	7.5	+0.3
IV	20	$2\,^{6}/_{12}$	10.0	23	—	10.3	+0.3
V	46	$4\,^{7}/_{12}$	10.4	49	$5\,^{2}/_{12}$	8.3	−2.1
			Spastics and other mentally deficient				
		1938			1948		in 10 years
107	9	—	6—7	19	—	7.4	+0.4—1.4
98	9	—	7.4	19	—	8.9	+ 1.5
110	11	—	9.0	21	—	11.3	+ 2.3
96	13	—	7.8	23	—	8.1	+ 0.3
109	13	—	8.7	23	—	8.8	+ 0.1
97	16	—	7.5	25	—	7.2	− 0.3
		1945			1948		in 3 years
VI	9	<2	7.0	12	$2\,^{5}/_{12}$	9.8	+2.8
VII	20	$3\,^{8}/_{12}$	9.5	23	$3\,^{3}/_{12}$	9.6	+0.1

Summary

Changes in the alpha frequency of the EEG over a ten year period have been examined in sixty normal cases. A comparison has been made with the corresponding changes in twenty-one pathological cases (mongols, spastics, mental deficients) and we have found a tendency to a less regular increase of the alpha frequency in the pathological cases.

Résumé

Les variations de la fréquence alpha des E.E.G. ont été examinées durant une période de dix ans dans soixante cas normaux. Une comparaison faite avec les variations correspondantes dans vingt et un cas pathologiques (mongoloïdes, spastiques, débiles mentaux) nous a montré une tendance à un accroissement moins régulier dans les cas pathologiques.

Zusammenfassung

Veränderungen in der Alpha-Frequenz der EEG wurden während eines Zeitraumes von zehn Jahren an sechzig Normalfällen untersucht. Es wurde ein Vergleich gezogen mit den entsprechenden Veränderungen bei einundzwanzig pathologischen Fällen (Mongoloide, Spastiker, geistig Zurückgebliebene). Wir fanden die Tendenz zu einer weniger regelmässigen Zunahme bei den pathologischen Fällen.

Sumario

Se ha examinado la frecuencia alpha en el electroencefalograma de 60 casos normales durante un período de 10 años. Hemos realizado un estudio comparativo con los cambios correspondientes a 21 casos patológicos (mongoloides, espásticos, oligofrenias) y hemos encontrado una tendencia a un menor aumento regular en los casos patológicos.

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FROM THE PAEDIATRIC CLINIC OF THE KRONPRINSESSAN LOVISA'S CHILDREN'S HOSPITAL, STOCKHOLM. CHIEF: PROF. A. LICHTENSTEIN.

Dermatitis Herpetiformis in Children

A report of three cases

by

Y. LARSSON and K. HÖÖK

Dermatitis herpetiformis (DUHRING) is a rare disease in children. This is especially the case in infancy where only single cases have been described. SÖBYE made a complete survey of the literature in 1945 and reported twenty-two own cases seen at the Dermatologic Department of the Rigshospital in Copenhagen since 1911. Among these four were infants of six to ten months of age. There were no new-born children in Söbye's material. According to MAC LEOD among 70 cases of dermatitis herpetiformis only six were children below 6 years of age.

In new-born children the disease has been reported by WILSON (1941), WILLI and BURCKHARDT (1941) and by ASBOE HANSEN (1947). The case of Wilson was a girl, with marked heredity for allergic disease, who got the skin eruption on the 3rd day of life, followed by an eosinophilia of maximum 59 per cent. In the case of Willi and Burckhardt the dermatitis began at the 1st day of life and the eosinophilia went up to as much as 83.5 per cent with leucocytosis to 39 400 white blood cells per cu.mm. Asboe Hansen described two cases. In the first one the disease started when the child was seven days old as a symmetrical multiform dermatitis with eosinophilia (37.5 per cent) and leucocytosis (43 800). The second case was two days old when the exanthema first appeared. The eosinophilia of that case was 40 per cent. These two cases showed a marked keratosis in the healing stages, already described as a typical sign by Duhring in 1884.

SELANDER in 1945 and IMERSLUND in 1948 have described four cases of »eosinophilia leukaemoides». It seems to us, however, that these were rather typical cases of herpetiform dermatitis with the same clinical picture as those cited above. They had all a symmetrical polymorphous exanthema with marked eosinophilia. They showed a chronic course but there was no fatal outcome. The eosinophilic cells were not pathological and the bone marrow was normal except for mature eosinophilia. We therefore think the term »eosinophilia leukaemoides» rather misleading in such cases.

All cases thus reported in literature have shown a similar clinical picture characterized by a symmetrical exanthema on the extremities and in the anogenital region. The onset is sudden with an outburst of vesicles containing clear liquid, rapidly developing secondary purulent infection. The vesicles become confluent and burst. The area becomes covered with yellowish crusts. Sometimes the lesion has a more maculo-papulous appearance. There is a circinate spreading of the exanthema in the periphery simultaneously with central healing. During the healing stages the skin becomes infiltrated, keratotic and pigmentated. Altogether there is a marked polymorphous character of the exanthema. Itching, being a common symptom in this disease in adults, is seldom seen in children. A constant sign in nearly all cases is the eosinophilia, occurring both in the blood and in the diseased skin regions. In the blood very high values of eosinophilic cells up to about 50 per cent may be observed. The course is chronic, each eruption lasting for 2—3 months but there is a marked tendency to relapses. However, serious complications seldom occur and the prognosis is favorable. In the following-up study of SÖBYE after about 20 years 50 per cent of the cases had recovered completely while 50 per cent still had symptoms. None had taken a fatal course. The etiology of this disease is unknown. The herpetiform appearance has given rise to theories of virus as the cause. The symmetrical localisation reminds of a neurological disease, although other neurological signs lack. The marked eosinophilia may indicate an allergic condition finally. The underlying causing mechanism is however still unknown.

In the Paediatric Department of the Kronprinsessan Lovisa's Children's Hospital three cases of dermatitis herpetiformis have recently been observed. One of them was in a new-born child, the other two in children of one and three years of age. They were characterized by a typical papulo-vesicular symmetrical exanthema, marked eosinophilia and a chronic course.

Case reports

Case 1.

M.A., a girl, was born on the 13th of October in 1948 and was admitted to Kronprinsessan Lovisa's Children's Hospital on the same day. She was dismissed from the hospital on the 5th of February 1949. Her father had a relapsing skin disease of three years duration, characterized by a patchy eruption on the arms and the trunk with symmetrical occurrence and only little itching. There were no vesicles or exsudation in the father. Nor did he show any eosinophilia. He had got the diagnosis of psoriasis in a dermatologic clinic. The mother had during pregnancy an itching exanthema that was diagnosed as scabies after delivery and then disappeared with ordinary antiscabies treatment. She had no eosinophilia. Wassermann's reaction was negative in both parents.

During delivery the amniotic fluid got a bloody colour. Because of this delivery was terminated by a forceps. The child had no asphyxia and cried vigorously, but it had copious tarry stools because of gastro-intestinal bleeding. It was supposed that this bleeding was the cause of the bloody colour of the amniotic fluid as there were no signs of abnormal bleeding from the mother. The child looked otherwise normal but was sent to our clinic immediately after the delivery because of its bleeding.

When first seen in this hospital physical examination showed a new-born girl, weighing 3 850 grams. The skin had normal colour and normal appearance. Respiration was normal. No cyanosis. Heart action was normal. There were no signs of intracranial haemorrhage. The abdomen did not show anything abnormal. A slight hypoprothrombinemia was corrected by giving vitamin K. Urine was normal. The haemoglobin content was 16.0 g per 100 cc and the red cell count 4 400 000 per cu.mm. The white blood cells amounted to 35 000. The differential count was normal, the number of platelets were 148 000 and the reticulocytes 3.4 per cent. During the first 24 hours there was still some blood in the stools but it then disappeared.

On the third day the skin lesion started as a massive eruption of papules occurring on the extremities. The papules soon became vesicular,

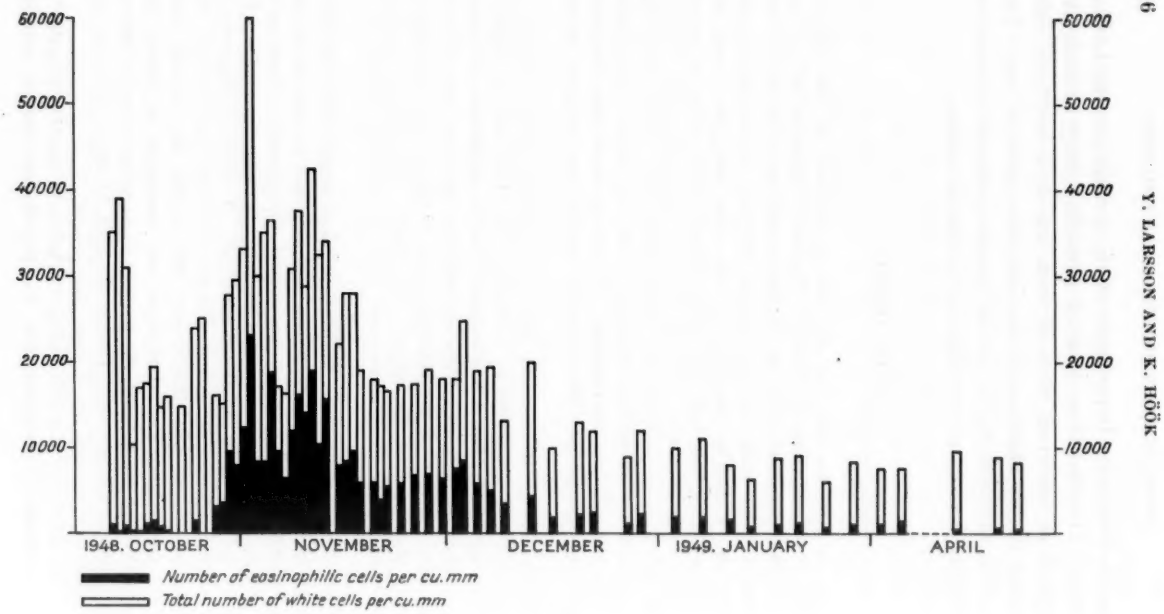
60000
50000
40000
30000
20000
10000
1948. OCTOBER
NOVEMBER
DECEMBER
1949. JANUARY
APRIL
Number of eosinophilic cells per cu. mm
Total number of white cells per cu. mm

Fig. 1.

confluent and ruptured. Bacterial culture from the fresh vesicles was negative, but after they had broken they became purulent because of secondary infection. After some week there was central clearing of the lesions with peripheral spreading and appearance of new papules and vesicles giving the lesion a circinate and a very marked multiform character. There were no signs of itching. The child's general condition was unaffected, she ate well and after four weeks of age started to gain weight normally. A few days after the first appearance of the skin disease eosinophilia was noticed in the blood together with a marked leukocytosis. The eosinophilia amounted to 54 per cent and the total white cell count to 60 600 cells per cu.mm. at most, see Figure 1. During the following two months the skin lesions healed very slowly, leading to a keratotic infiltration of the skin, in some places covered by dry crusts. A brownish pigmentation on the extremities was the only remaining residue of the disease. The eosinophilia and leukocytosis disappeared subsequently. There was no enlargement of the liver, the spleen or the lymph nodes during the course of the disease. Roentgenographic examination of the lungs and of the bones showed nothing abnormal. Sternal marrow was normal except eosinophilia. No pathological or immature white blood cells were seen. Wassermann's reaction was negative. Sedimentation rate was normal in the beginning but rose slowly to values about 25 mm per hour.

Penicillin was given intramuscularly to prevent secondary purulent infection but had no effect on the basic disease. An anti-histamine drug (Antasten Ciba) was also given for a long time without effect. Otherwise no treatment was given. As cases of herpetiform dermatitis are said to be sensible to iodine an attempt to provoke new skin eruptions was made with this drug when the disease was in the healing stage but without any effect.

Case 2.

S.L.F., a three year old girl, was admitted to the clinic on the 21st of April 1949 and dismissed on the 24th of September 1949. Members of the father's family had asthma but otherwise she had no heredity for allergic or skin disease. She had always been well until the beginning of February 1949 when she suddenly got an eruption of impetiginous vesicles in the face and on both arms and legs. Her father had impetiginous lesions on the skin of the legs at the same time. Some of the vesicles of the child were bigger than is ordinarily seen in impetigo, had a very thin wall and contained a clear liquid. They soon became purulent and confluent and ruptured. She was admitted to the children's department of a local hospital where the diagnosis of impetigo contagiosa was suspected. Treatment with ordinary ointments and penicillin intramuscularly rendered an improvement which however was soon followed by a relapse. The primary lesions seemed to clear up centrally but

there were new eruptions in the periphery. The general condition was good. It became clear that the child suffered from some kind of unusual skin disease among which herpetiform dermatitis was suspected and after three months she was sent to Kronprinsessan Lovisa's Children's Hospital.

On admission she was in a good general condition without signs of cardiac, pulmonary or abdominal disease. There was a symmetrical maculopapulous eruption on the skin of the limbs, especially the feet, the hands and forearms, and in the anogenital region, on the buttocks and in the vulva. There were signs of central healing with peripheral spreading. In the margins there were unruptured pustular vesicles. Because of clear evidence of bacterial infection — culture from the skin lesions showed abundant growth of staphylococci and streptococci — penicillin was given intramuscularly. The pustular picture then rapidly disappeared and the lesions again seemed to heal. However, new eruptions soon occurred and the primary lesions showed to be a rather great vesicle on normal skin with a thin wall and containing a clear and sterile liquid. The picture was somewhat similar to that of pemphigus vulgaris but more polymorphous and variable. Each eruption was followed by secondary bacterial invasion. Her general condition was good during the whole time and there was no itching. The blood showed a normal number of white blood cells with values about 8 000 per cu.mm. She had a moderate eosinophilia amounting to 20 per cent during the acute stages. The antistreptolysin titre was elevated, 800 antistreptolysin units per cc, and remained high. The antistaphylolysin titre became markedly elevated, 8 units per cc. Wassermann's reaction was negative. — Attempts were made to provoke an attack with iodine but without any result. Arsenic trioxide in doses from 0.5 mg increasing to 5 mg per day was given for a period of three weeks in August 1949. The remaining exanthema rapidly disappeared and did not return when the treatment was discontinued. If this effect was due to the arsenic or coincidental is however impossible to say, as the disease had already shown a tendency to heal out. Each eruption had been milder than the foregoing. After six months' stay in the hospital the child could finally be sent home in a very good condition without active skin changes.

Case 3.

S.H.F., a 13 months old boy, was admitted to the hospital on the 1st of July 1949 and dismissed on the 10th of October 1949. The history revealed a normal delivery. He had no heredity for allergic diseases. He had been breastfed six months and had developed normally. He had seemed to be hypersensitive to oranges but otherwise he had shown no signs of allergy. When seven months old he had a rash on the cheeks, which disappeared after one month.

At about 12 months of age he got a mild acute gastroenteritis and two weeks later the skin lesions started. Without other symptoms of

Fig. 2.

illness blisters appeared on the skin, starting on the cheeks and chin but soon spreading to the trunk, the groins and calves. They had thin walls and contained a clear fluid. The surrounding skin area showed no alterations. The vesicles soon ruptured and yellowish crusts were formed. There was no itching. He came to the hospital after he had had these eruptions for four weeks. His general condition was good. His weight was 11.4 kg and his height 73 cm. Apart from the skin lesions physical examination showed nothing abnormal. The skin showed a cherry-red exanthema with papules and vesicles, the size of a pea, symmetrically localized on the chin, the abdomen, the genitals and on the inner sides of the thighs. The eruption had a sharp outer limit but in its neighbourhood a few single fresh blisters could be seen on normal skin. They contained a clear fluid which on culture proved to contain Streptococcus viridans and Staphylococcus aureus. The same organisms were found in the older lesions. The Fig. 2 shows the appearance of the skin in this case. In the virus department of the State Bacteriological Laboratory (Prof. S. Gard) attempts were made to cultivate a virus from the vesicle-content but with negative result due to formation of inhibiting toxins from the staphylococci. Blood examination showed a moderate leucocytosis amounting to 20 000 white cells per cu.mm. As in case 1 the eosinophilia of the blood was very marked and long-standing. It amounted to at most 49 per cent. The boy was treated with penicillin intra-

muscularly and locally without much effect. After some weeks' apparent improvement new eruptions occurred with immediate bacterial invasion. During the healing stages the leucocytosis and eosinophilia decreased but reappeared during the relapses. After four weeks' stay in the hospital the boy was practically in the same condition as when admitted. We then decided to make an attempt with arsenic treatment and thus gave him arsenic trioxide by mouth beginning with 0.5 mg per day and slowly increasing the dose to 5 mg per day. This treatment was given for four weeks and during that period there were obvious signs of improvement, the older lesions healed and new eruptions did not appear. When the arsenic drug was omitted the patient got a relapse. Improvement when arsenic was given and exacerbation when it was withheld was observed twice. After three months' stay in the hospital the disease had taken quite a mild character and seemed to be under satisfactory control.

Comment

In the first case the diagnosis of herpetiform dermatitis could easily be established. The symmetrical localization of the skin lesion, its multiform appearance, the chronic course and the marked eosinophilia were typical for this disease. Similar conditions as pemphigus vulgaris, impetigo contagiosa or syphilitic skin disease could be excluded without difficulty. The assumption of a hereditary cause of the disease was in this case supported by the fact that the father had a chronic skin disease, probably psoriasis. That the scabies of the mother during pregnancy played any role as sensitizing factor is unlikely but cannot be judged. Nor do we know if the gastro-intestinal bleeding of this patient, starting already in utero, had any connection with her skin disease.

The second case was not as typical as Case 1. The vesicles resembled pemphigus more than would be expected in dermatitis herpetiformis, but the polymorphous appearance of the lesions, their symmetry, the chronic course without disturbance of the child's general condition and the eosinophilia established the diagnosis. No conceivable etiologic factor except an allergic disposition in the father's family could be found and therapy could only be symptomatic. The high antistreptolysin titre and antistaphylolysin titre were most likely due to the longstanding secondary infection of the lesions.

In Case 3 the vesicular component was more marked than in the first case, too. Otherwise it seemed to us to be a very typical case of dermatitis herpetiformis. The longstanding high degree of eosinophilia was remarkable in both the first and third cases. Earlier reports of beneficial effect of arsenic treatment in dermatitis herpetiformis support the view that the good result of arsenic in Case 3 was no accidental coincidence. Viral etiology of dermatitis herpetiformis would seem a possible theory and the symmetrical distribution might suggest a neurotropic virus. An attempt to demonstrate a virus in Case 3 was however negative, possibly due to inhibiting activity of bacterial toxins. In cases with less pronounced secondary infection similar attempts may be more successful.

Summary

Three cases of dermatitis herpetiformis in children are described. The first case, a new-born child, is remarkable as the disease is very rare in the neonatal period. All the cases were typical with a symmetrical multiform eruption, a chronic course without affection of the general condition and with a marked longstanding eosinophilia of the blood.

Résumé

Trois enfants avec dermatite herpetiforme sont décrits. Le premier cas, une nouveau-née, est remarquable puisque cette maladie est très rare dans cet age. Tous les cas ont été typiques avec une eruption symétrique et multiforme, un cours chronique sans influence sur la condition generale des enfants et une éosinophilie du sang considérable et de longue durée.

Resumen

Se describen tres niños con dermatitis herpetiforme. El primer caso, una recién nacida, es notable puesto que esta enfermedad es muy rara en tal edad. Todos los casos se han caracterizado por una erupción simétrica y multiforme, un curso crónico sin influencia sobre las condiciones generales de los niños y una eosinofilia de la sangre considerable y de larga duración.

Zusammenfassung

Drei Fälle von Dermatitis herpetiformis bei Kindern sind beschrieben. Der erste Fall, ein neugeborenes Kind, ist besonders bemerkungswert, als die Krankheit sehr selten in den ersten Lebenswochen ist. Die Fälle waren alle typisch mit symmetrischen, polymorphen Eruptionen, kronischem Verlauf ohne Störungen des Allgemeinzustandes, und mit ausgesprochener langdauernder Eosinophilie im Blute.

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FROM THE PAEDIATRIC CLINIC OF KAROLINSKA INSTITUTET AT KRONPRINSESSAN LOVISA'S CHILDREN'S HOSPITAL, STOCKHOLM.
CHIEF: PROF. A. LICHTENSTEIN.

Determination of the Circulation Time in Children by the Decholin Method

by

JOHN LIND

Determination of the circulation time has long been known as one of the methods employed for investigating the circulation, and it has been in use among scientists for some time. It is only during the last two decades, however, that the technique has been simplified sufficiently to allow the test to be brought into routine use in hospitals and in private practice. There are at present several simple and accurate methods from which to choose. A large series of investigations has been carried out on adults, some in perfectly good health and some suffering from ailments that could be expected to affect the circulatory system. Determination of the circulation time has been found of value especially in the diagnosis of retardation of the blood flow, in the therapeutic guidance of circulatory insufficiency, and in the early recognition of conditions of non-cardiac origin (pulmonary dyspnoea, obstruction of the superior or inferior vena cava, anasarca of hypoproteinaemia, etc.).

Through the discovery of a new sphere of use for determinations of the circulation time more attention has been paid to them in recent years, since it has been found that a veno-arterial shunt can be demonstrated by this method. When this is present, a short circuit takes place in the blood circulation and the circulation time is reduced. A similar shunt mechanism is found quite frequently in cases of congenital vitium cordis and a number of such cases have been described (TARR and COLLABORATORS 1932,

KAISER 1936, MCGUIRE and GOLDMANN 1937, MANNHEIMER 1944, KADENAS 1940).

Retarded circulation from the arm vein to the lung and up to the tongue is usual in patients with enlargement of the right side of the heart and in those with incompensation. If, however, the circulation time for both these stretches is equal, this indicates the presence of a shunt, as, for example, in cases of transposition of the large vessels, tetralogy of Fallot, and Eisenmenger complex. Occasionally a defect of the septum auricularum may give rise to the same phenomenon.

Thus a study of the circulation time has often proved of interest in cases of congenital vitium cordis and nowadays as a rule the circulation time is determined in advance, in angiocardiographic examinations, in order to decide the moment when the exposure should be made.

To sum up, it can be said that notwithstanding theoretical objections, determination of the circulation time has proved a valuable test of haemodynamic conditions of the cardio-vascular system because of the narrow range of circulation times in health and the characteristic alterations in disease.

It is therefore remarkable that so few investigations should have been carried out on children, especially in view of the fact that there is need for satisfactory tests for the function of the heart which can be applied to children for discovering latent cardiac insufficiency.

Very few investigations have been carried out for the purpose of obtaining the normal values for the circulation time in children, and there is still uncertainty both as to what these values are and to whether significant differences exist between different age groups.

Methods Available

A large number of methods for determining the circulation time of the blood have been in use for some time.

The following five requirements must be met before a substance can be employed for determining circulation times (BLUMGART and YENS 1927).

1. The substance must be non-toxic in the concentrations which are to be used.
2. It must be easily demonstrable.
3. It must not disturb the phenomena to be studied.
4. The substance must be secreted quickly from the body in order to permit of a fresh investigation after a short time.
5. It must have a marked effect even in small quantities (and the same effect in pathological cases), so that the injection can be made speedily and the substance transported in a small volume of blood, with the result that both injection and apperception will be instantaneous.

Various *pigments* have been tried, examples of these being methylene blue (STEWART 1921—22, E. KOCH 1922), brilliant vital red (THOMPSON and COLLABORATORS 1928, HAMILTON and COLLABORATORS 1928), Congo red (KLEIN and COLLABORATORS 1929) and fluorescein (KOCH 1922). The colouring matter was injected into the vein of one arm and its arrival in the forearm of the opposite side was determined by taking frequent samples of blood.

The fluorescein method was later adopted in a modified form by WOLLHEIM and LANGE (1931), who devised a method for demonstrating the fluorescein in the intact vascular system. They discovered that if ultra-violet rays were employed, the fluorescein could be seen through thin mucous membranes when it flowed into the fine vessels. The method was later used by LANGE and BOYD (1942), and in children by WITZBERGER and COHEN (1943). A further modification of the technique has been introduced by NATHANSSON and MERLISS (1943). Instead of observing the fluorescein on a mucous membrane, they used one or more histamine-wheele by means of which the position of the terminal point could to a certain degree be selected. The method is stated to be »objective», but the appearance of the fluorescein is not always so marked that it permits of exact registration, but instead depends to a certain extent on the experience and judgement of the observer.

Using small quantities of *radio-active substance*, it became possible for the first time to determine the circulation time from the site of injection to the right auricle and from there through

the lungs to the other arm (BLUMGART and COLLABORATORS 1927). Since then, additional objective methods for scientific use have been described. Thus NYLIN and COLLABORATORS (1943) used red blood corpuscles marked with radio-active isotopes. MCCRACKEN, ESSEX, and SHEARD (1937) determined the circulation time in dogs by an ionization method, with a Geiger counter as detector. LYSHOLM and his collaborators (1943) employed »activated sodium chloride», which emits powerful γ-radiation. This method was well suited to determination of the circulation time to peripheral vessels, both arteries and veins. In order to determine the circulation time to the heart and the great central vessels, LYSHOLM devised a roentgenological method. An opaque substance (perabrodil) was injected into the left cubital vein and had to pass two Geiger-Müller counters, the passage of the substance past the first counter setting in motion a clock that was stopped when the substance passed the second.

Other methods have been tried for practical clinical use. TEPLOW and SOOR (1938) introduced alpha-*lobeline,* which, when it reaches its destination, results in an instantaneous deeper intake of breath. The values obtained with this method, used on adults, are strikingly low, approximately the same as those obtained with HITZIG's method of injecting ether intravenously to measure the circulation time (from the arm to the lung). This has been pointed out by VESA and caused him to suspect that the lobeline directly affects the lung and does not act via the coughing center or the sinus caroticus. The method has been applied to children by GRANDI (1941), who recommends it and considers it superior to both the decholin and calcium gluconate methods. LILIENFELD and BERLINER (1942), making duplicate tests on one hundred patients between the ages of fourteen and seventy-three with this method, obtained strikingly large differences. In the group with healthy hearts, the circulation time was on an average 9.5 seconds; the range of variability 4.9—16.5 seconds; and the mean difference between the first and second test 20 % (of the first value). As far as was possible, the tests were carried out under identical conditions. The time interval between the two tests was fifteen—twenty minutes.

Sodium cyanide was found by LOEWENHART and his collaborators (1919) to have a similar effect to lobeline, i.e. it stimulates the respiration center, possibly via the sinus caroticus. The effect occurs suddenly, which makes it possible to use it in the same way as lobeline (ROBB and WEISS 1933). As is the case with lobeline, sodium cyanide is not altogether harmless (JABLONS 1943). The lethal dose is stated to be only ten times as much as the stimulating dose. Furthermore, the breathing of small children, especially if they are restless, is often so irregular that the reaction can be negligible. Nicethamide in a 25 % solution has also been used similarly (RUSKIN and ROCKWELL 1945) on small children, but was abandoned as it frequently (in approximately 20 % of the cases, RUSKIN and DECHERD 1946) does not give any reaction (inspiratory gasp and a subjective burning of the face). Aminophylline and papaverine which, when injected intravenously, have a similar effect, have also proved to be too unreliable and have therefore been abandoned (RUSKIN and DECHERD 1947).

Investigations with *histamine* (WEISS, ROBB, and BLUMGART 1929) may also be mentioned among the objective methods. This substance produces when injected intravenously sudden burning of the face and at the same time a metallic taste on the tongue. The normal values for adults show a striking variation (thirteen —thirty seconds). A later modification of the method (dilution of the histamine) has resulted in lower and more even values (WINTERNITZ, DEUTSCH, BRÜLL 1932). The method has proved to have great disadvantages, since it often produces intense headaches, dyspnoea, and sometimes collapse due to failure of the circulation.

In heart failure it may be useful to know in which segment the blood flow is retarded and attempts have been made to study the circulation time in the two main segments of the circulatory pathway. By injecting ether and measuring the time from the moment of its being injected until its smell is apparent in the breath expelled, it is possible to get an idea of the circulation time between the left cubital vein and the capillaries of the lungs via the right half of the heart (HITZIG 1935).

In order to measure the circulation time between the capil-

laries of the lungs and the periphery, a method has been worked out by MATTHES and MALIKIOSIS (1936). They placed a photocell with a light source on the ear or in a fold of the skin. The patient was then required first to hold his breath or to inhale a compound with a low oxygen content for a short while and then to take a deep breath of ordinary air or oxygen. The circulation time from the capillaries of the lungs via the left half of the heart to the skin is then equal to the interval between the start of the inhalation and the arrival of the oxygenated blood at the photocell.

One year earlier, a similar method had been proposed by GUBNER and his collaborators (1935). They required the patient to inhale carbon dioxide and measured the time from the commencement of inhalation until the reaction was evident in the form of a sensation of warmth in the head and an instantaneous increase in the depth of the breathing.

Photoelectric cells have been used also in another way for determination of the circulation time. If a substance such as methylene blue is injected it obscures the light as it passes the photocell. In this way it is also possible to determine the time which elapses before the substance leaves the place of destination, as well as the circulation time to various parts of the skin (JABLONS ET AL. 1943).

In 1922 HIRSCHSOHN and MANDEL introduced *calcium chloride*. This produces a sensation of warmth in the skin and a burning in the throat. Owing to its toxic side-effects (above all on the heart) it has proved unsuitable, however. Calcium gluconate has been used for investigations carried out on children (GRANDI 1941). Magnesium sulfate has also been used (SPIER and COLLABORATORS 1936, BERNSTEIN and SINKINS 1939, VESA 1941); this produces a sudden sensation of heat, first in the face, then spreading to the hands and soles of the feet. This substance should thus provide the possibility of studying the arterial blood flow at the periphery. If any of the substance is injected paravenously a burning pain results and persists for several hours (KVALE and ALLEN 1939).

Substances producing sharp taste sensations have also been tried, for example *saccharin* (FISHBERG and COLLABORATORS 1933).

Duplicate determinations have been carried out with this substance in a large series of cases (ESSER and BERLINER 1943), namely in a total of sixty patients, thirty four of whom had healthy hearts. The tests were carried out under identical conditions as far as possible, with an interval of one hour between the two. The results did not agree well — »agreement was the exception, considerable differences were the rule». The method has moreover the drawback that saccharin beside a vein gives rise to persistent infiltrates. Another substance which, when injected, results in a strong taste in the mouth and which has therefore been adopted is thiamin (RUSKIN and DECHERD 1934). However, the range of variability with this method is suspiciously wide (5—13 seconds), and the lowest values agree better with those obtained when measuring the circulation time from the arm to the lungs. *Decholin* was introduced in 1931 by WINTERNITZ and his collaborators. This substance gives an instantaneous and concentrated bitter taste in the mouth, though it is of short duration. Many objections have been raised against this, as against all other »subjective» methods, since it requires cooperation from the patient and such factors as the speed of the patient's reaction may play a part.

In spite of this, it has been more or less generally adopted, and satisfactory results have been obtained with it in practice (TARR and COLLABORATORS, NYLIN, KREMER and ROBERTSON, MACY and COLLABORATORS, CANDEL and RABINOWITZ, MANNHEIMER, etc.). It is simple to use, seldom fails, and appears to be sufficiently accurate for practical use, a fact that has been demonstrated in parallel series with »objective» methods, the cyanide and histamine methods (GARGILL, VOGTLIN and COLLABORATORS, WINTERNITZ and COLLABORATORS). It is very seldom that no taste sensation occurs or that it is slight. With duplicate tests, the values agree well and the range of variability for the normal values is comparatively small, and thus in this respect it compares favourably with the radium, histamine, lobeline, and saccharin methods. TARR, OPPENHEIM, and SAGER established »remarkable agreement in duplicate tests on normal individuals with differences not exceeding three seconds».

GARGILL carried out triplicate tests on more than one hundred and fifty individuals and stated that »thrice measurements usually checked within one second or a fraction thereof». It has been stated that the method is not altogether without danger. Toxic reactions were reported by LEYS. One fatal case was reported as occurring immediately after a test (MACY and COLLABORATORS 1936). However, an overwhelming majority of authors have had no unpleasant experiences with it. NYLIN has employed the method widely for many years and on only one occasion has experienced unpleasant complications, namely incipient oedema of the lungs in a strongly vasolabile individual in connection with the second injection, made ten minutes after the first. Should the injection happen to be made paravenously, slight pain is experienced for some hours, but there is, on the other hand, no risk of necrosis or thrombosis, as when calcium salts are used. The value of the method has been further increased as a result of NYLIN's work. He demonstrated the connection between the length of the circulation time and the amount of blood left in the heart, and also the fact that by measuring the duration of the taste sensations, the amount of blood left in the heart could be gauged (NYLIN-MALMSTRÖM 1941), a modification of the test which unfortunately cannot be applied to young children.

Earlier Investigations on Children

In a comprehensive investigation, W. VIERORDT (1858) found that the circulation time via analogous vessel sections in different animals was in direct relation to the size of the animal, the average circulation time from the vena jugularis externa and back to the starting point corresponding to the time for twenty six—twenty nine heart beats. With this as a basis, he calculated the circulation time for adults and for children (1877). He divided them into four different age groups and obtained the following values:

	Weight kg	Pulse	Circulation Time sec
Newborn	3.2	134	12.1
3 Years old	12.5	105	15.0
14 Years old	34.4	87	18.6
Adult	63.6	72	22.6

Since then a few investigations have been carried out on children, but as yet their number is not very great. The results are summarized in Table 1.

SECKEL injected histamine in the longitudinal sinus; the values he obtained were higher than those usually given.

HUBBARD's material is extremely heterogeneous and cannot be regarded as normal; it includes »a variety of medical diagnoses, both cardiac and non-cardiac».

A few older children are included in the series of KOCH and BLUMGART and COLLABORATORS (children between the ages of twelve and fifteen years). The circulation time for them was about twelve seconds, being the same as the lowest normal times for adults.

Some Factors Affecting the Normal Values with Respect to the Circulation Time

Technique

By using different doses of decholin, magnesium sulfate, thiamine, and aminophylline, RUSKIN and ROCKWELL (1945) were able to show that small doses either do not produce any reaction at all or else give values for the circulation time that are too high. The optimal dose was established for the various preparations. For example, for adults the decholin dose should exceed 0.50 g (2.5 ml of a 20 % solution). Regarding the volume of the substance injected, it was found that this also affected the circulation time; if a relatively large volume is injected, lower values for the circulation time are obtained, probably depending on the fact that a speedy injection increases the rate of circulation in

the first part of the vessel section. RUSKIN and ROCKWELL assume that the widely varying values obtained by different methods can to a large extent be explained by the fact that the doses injected and the quantity were insufficient.

Other Factors

A striking feature is the relatively insignificant difference in the circulation time between children and adults. This was also foreseen by TARR and his collaborators. The same condition has been found in experiments with animals. Thus MCCRACKEN and his collaborators (1937) found when investigating the circulation time in dogs using the ionization method (Geiger counters) that there is no relation between the circulation time and the age, sex, or weight of the animal.

In WEILL-HALLÉ's investigation, comprising the age group seven—thirteen years, no fixed relation was evident regarding age or sex, nor pulse and respiration. The shorter circulation time for children was attributed to the higher rate of metabolism.

SECKEL found that important factors governing the circulation time in healthy children were the size of the body, age, and nutritional condition, in the order given here. Older children with a low weight had a longer circulation time than younger, normally-developed children of the same weight. Further, he found lower values for dystrophic children than for healthy children of the same age.

Here it may also be of interest to mention some of the results obtained in adults by BLUMGART and COLLABORATORS (1927—1930). They found that the circulation time increased considerably with increasing age. For the age groups between fifteen and twenty nine years, it was twelve—twenty three seconds (average seventeen sec.), while for the higher age groups it remained more constant, or sixteen—twenty one seconds (average nineteen sec.). It was, furthermore, also noted that the circulation time decreased to an insignificant extent in connection with a markedly increased heart frequency, and that it did not appear to be influenced at all by normal variations in venous and arterial pressure. These

Table I

Method	Author	No. of Cases	Age in Years	Mean (sec.)	Range of Variability (sec.)	Adults		End-Point
						Mean (sec.)	Range of Variability (sec.)	
Histamine	Seckel 1931	22	0—1	14.9	14—17	23	13—30	Skin
		15	1—2	17.6	13—22			
»	Weiss et al. 1929	30	10—19	18	13—22			
Fluorescein	Witzberger & Cohen 1943	51	0—2	11.5	8—16			Lips
		25	3—13	7.0	5— 9.1			
Radio-Active Sodium Chloride	Hubbard et al. 1942	14	0—2	7.0	3—12			Vein in hand
		22	2—12	11.0	5—17	18	14—24	Vein in cubital reg.
Natrium Cyanide	McGuire & Goldmann 1937	11	7—12	19.6	9—14.5	15.6	9—21	Sinus caroticus
Calcium Gluconate	Grandi, F., 1941	30			7.5—16	12.4	10—16	Tongue
Lobeline	Grandi, F., 1941	115	3—12	6.2	3—12		6—13	Sinus caroticus
Saccharin	Averbrück and Friedman 1935	100	8—16	8.6	5—13.5	13	9—16	Tongue
»	Weill-Hallé & Facquet 1937	14	7—13	11.2	7.5—14			»
Decholin	Mannheimer 1941	16	6—15	±0.8 10.75		±12.8 0.22		»
»	Grandi, F., 1941	30			9.6—20			»
»	Tarr	6	10—14	13	12—17			
Thiamine	Ruskin & Decherd 1947	17	5—12		4— 8			

If nothing is stated to the contrary the time was recorded from the moment of injection.

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Other Factors

A striking feature is the relatively insignificant difference in the circulation time between children and adults. This was also foreseen by TARR and his collaborators. The same condition has been found in experiments with animals. Thus MCCRACKEN and his collaborators (1937) found when investigating the circulation time in dogs using the ionization method (Geiger counter) that there is no relation between the circulation time and the age, sex, or weight of the animal.

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		22	2—12	11.0	5—17	18	14—24	Vein in cubital reg.
Natrium Cyanide	McGuire & Goldmann 1937	11	7—12	19.6	9—14.5	15.6	9—21	Sinus caroticus
Calcium Gluconate	Grandi, F., 1941	30			7.5—16	12.4	10—16	Tongue
Lobeline	Grandi, F., 1941	115	3—12	6.2	3—12		6—13	Sinus caroticus
Saccharin	Averbrück and Friedman 1935	100	8—16	8.6	5—13.5	13	9—16	Tongue
»	Weill-Hallé & Facquet 1937	14	7—13	11.2	7.5—14			»
Decholin	Mannheimer 1941	16	6—15	±0.8		±12.8		»
				10.75		0.22		
»	Grandi, F., 1941	30			9.6—20			»
»	Tarr	6	10—14	13	12—17			
Thiamine	Ruskin & Decherd 1947	17	5—12		4— 8			

If nothing is stated to the contrary the time was recorded from the moment of injection.

results were later confirmed by other investigators (among others by TARR and COLLABORATORS and by KVALE and ALLEN 1939). It was proved that the sex, height and weight, body surface, and vitality of the patient did not affect the circulation time. Neither did it appear that the circulation time was affected by the patient's mental condition.

KVALE and ALLEN found that the circulation time was reduced during digestion and during bodily exertion (crying and motorial unrest in young children should therefore also result in an increase in the rate of circulation). Further, they found that the speed of the blood flow in the arteries increased with rising temperature of the skin.

In order to throw light on certain sources of error inherent in determinations of the circulation time in children, HUBBARD and his collaborators carried out comparative investigations on two infants while at rest, after exertion, and finally with a closed glottis after deep inhalation (heightened intrathoracal pressure). In the last-named case considerable prolongation of the circulation time was noted, while there was a very slight reduction after exertion.

Many authors consider that the shorter distance the substance is required to travel in children also contributes to some extent to the fact the values for the circulation time are lower.

Material

The investigation in question was undertaken in the spring of 1942 at Kronprinsessan Lovisa's Children's Hospital.

The number of cases investigated amounted to 182 children without any sign or previous record of illness which could be thought to affect the circulatory system.

All the children examined had sound hearts. They had been admitted to the hospital for psycho-examination (enuresis, refusal to eat, etc.), worms, and similar ailments. With the cooperation of the Superintendent of the surgical wards it was possible to examine the children admitted there; in most cases they were under observation for abdominal disorders but some were fracture

cases. All of the children were free from fever, and their past history contained no mention of infections likely to have resulted in injury to the heart. A fair number of the children had had a slight soft systolic murmur, most prominent over the base. In all these cases (56) both an electrocardiogram and a phonocardiogram were made (by MANNHEIMER's method).

Technique

All the children were examined under standard conditions, viz. on an empty stomach in the morning before they had started their play. In the ESSER and BERLINER investigation, in 1943, where duplicate tests were made with the saccharin method, it was shown that the difference was considerably less if the patient was in a so-called basal condition. As far as was possible, the injections were given at the same speed in all cases, but in view of the varying caliber of the veins this was not always successful. Stasis was produced for the shortest possible time. Before the circulation time was determined, it was necessary for the reaction from the pain of injection to have passed so that the child breathed calmly (if the patient holds his breath the venous flow to the heart is retarded, hyperventilation on the contrary increases the venous flow). The child was prepared in advance for the bitter taste and was told to say immediately when this was experienced. In cases where the child did not do this, the momentary mimetic reaction made it possible to register the appearance of the taste in the mouth. It was possible to use only thin needles on account of the narrow veins of the children. The injection took two to three seconds to perform. Because the injection is not instantaneous and the volume of the substance injected is so small, its mechanical effect in reducing the circulation time should be of little account. Each child was placed in a fully horizontal position with the arm placed so that the point of injection in the vein lay on a level with the anterior axillary line. The time elapsing from the start of the injection until the patient reacted to the bitter taste was recorded by an assistant with a stopwatch. In accordance with the directions of TARR and his collaborators,

the time was taken at the start of the injection rather than at the conclusion, lest the response come with a minimum amount of the drug. The dose of decholin was 2 ml for children under seven years of age and 3 ml for older children. In all cases a definite response was observed. In about ten cases the children screamed after the injection or were so disturbed that it was not possible to examine them. No complications or unpleasant experiences occurred except that in a few cases transient epigastric pains were experienced. In a number of cases the first value obtained was again checked. In most cases the blood pressure and the rate of respiration were taken immediately before the test. The pulse was recorded immediately before and after. Originally, saccharin was chosen (50 % sterile solution, 2 ml for small and 3 ml for older children). In many cases, however, no distinct reaction was obtained, and decholin was therefore used in preference. HUBBARD and COLLABORATORS (1942) also had less satisfactory experience with saccharin when used on children.

Results

The results of the investigation have been summarized in the following table. Boys and girls have been grouped together, since no difference in the sexes as regards circulation times has been demonstrated.

Age in yrs.	Number	Mean ± E_M	Standard Deviation		M ± 2.5 σ	Range
			Sec.	% of Mean		
3— 6	24	10.5±0.21	1.01	9.62	8.0—13.0	8—12
6— 9	65	10.4±0.18	1.48	14.23	6.7—14.1	7.5—15.5
9—12	67	11.0±0.16	1.32	12.0	7.7—14.3	7.5—14
12—15	26	11.9±0.39	2.00	16.81	6.9—16.9	10—16

In fifty two cases a duplicate test was made after an interval of about five minutes. The mean error in the method, calculated in the usual way from the duplicate tests, was 7.8 per cent.

The circulation time bears a closer correlation to the weight than to the height. As regards the relation of the circulation time to age, there is a tendency towards an increase with increasing

age; when calculated it was found to be equal to 0.16 ± 0.04 seconds. The increase is statistically significant for the mean. There is only a slight positive correlation between the circulation time and the body surface (no correlation for a body surface up to 0.90 sq.m. and a slight positive correlation for higher values).

No relation between the circulation time and the blood pressure (arterial and venous) was established, nor did the pulse or respiratory frequency have any relation to the circulation time.

Finally, it can be stated that comparative determinations of the circulation time were made in ten children between the ages of ten and fifteen years in both the recumbent and erect positions. Of these, four were normal children and four had an orthostatic reaction with an increased pulse rate above 40 in the erect position and electrocardiographic changes of the typical kind. In the erect position the injection was made after six minutes and with the arm resting on a horizontal support. All the normal children showed a reduction of the circulation time by one—three seconds; one of the orthostatic cases showed an unchanged circulation time and three a slight increase (from eleven to thirteen, eleven to fourteen, and ten to thirteen seconds, respectively) and one case a considerable increase from twelve to seventeen seconds. Two of these children felt sick and vomited after the decholin injection in the erect position, and the investigation was therefore discontinued.

Summary

A short account is given of current methods for determining the circulation time. Using the decholin method, 182 children between the ages of three and fifteen years were examined; the results are analyzed statistically and the error in the method calculated from duplicate tests.

Résumé

Un résumé des méthodes courantes de détermination du temps de la circulation est donné. 182 enfants, de 3 à 15 ans, ont été examinés au moyen de la méthode décholine; les résultats sont calculés statistiquement et l'erreur de la méthode est calculée à l'aide de tests doublés.

Zusammenfassung

Ein kurzer Bericht wird gegeben über die gebräuchlichen Methoden zur Bestimmung der Umlaufszeit. Unter Anwendung der Decholin-Methode wurden 182 Kinder zwischen 3 und 15 Jahren untersucht. Die Resultate wurden statistisch analysiert, und der Fehler in der Methode wurde mittels doppelter Versuchen berechnet.

Sumario

Se da un breve informe sobre los métodos corrientes para determinar el tiempo de circulación. Usando el método decolino, se examinaron 182 niños de entre 3 y 15 años; se analizan estadísticamente los resultados y se calcula el error del método mediante ensayos duplicados.

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Unilateral Nystagmus in Infancy

by

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Unilateral nystagmus (N) is a rare disorder that may occur in children as well as in adults in association with diseases of the CNS or amblyopia monocularis, but it may also occur as an isolated dysfunction in infants without any concomitant cerebral or ocular defect's being demonstrable. A survey of the literature shows that unilateral N of the last-mentioned type is very rare indeed. According to RABINOWITSCH, only forty pure cases were reported up to 1926 — i.e., cases in which no involuntary movements were observable in the other eye. Since then only six cases have been reported (POST (1), RABINOWITSCH (2), ØSTERBERG (2), and MOORAD (1)). At the Paediatric Clinic, Lund, four cases of unilateral N have been observed during the last few years. In one of these cases, however, N developed subsequently in the other eye also. In the following these cases will be described and commented upon.

Case I was a six mo. old boy who had had left N for one week, but was otherwise quite healthy. Examination on admittance showed a well-developed child with left N of the pendulating type. His visual acuity was apparently good. Skiascopy: r. $+ 4.0 - 1.5 \times 180$. l. $+ 4.5 - 2.0 \times 180$ Fundi[1]: normal. Caloric test: nothing path. Lumbar puncture: normal liquor finding. After about one month the patient also developed right N, after which the picture tended to change, N most often being bilateral and synchronous, but sometimes more conspicuous in one eye or the other. Furthermore, it was noticed that N disappeared in sleep and that it did not recur until after fifteen—thirty seconds' fixation. N gradually disappeared after about three and a half months.

[1] The ophthalmological examinations in this case and in the following were performed by eye specialists.

Earlier this type of N was considered to be connected with all sorts of diseases, such as rachitis, lues, epilepsy, etc. Many authors believe it to be an isolated symptom of spasmus nutans, a disease the main symptom of which besides N is a nodding and rolling of the head. This disease, which has been thoroughly described by RAUDNITZ (1897), is an anomaly found particularly in infants six to twelve months old. It never disturbs the physical or mental development. A typical feature of this disorder is that it disappears when the baby is asleep. N is said to be unilateral in about 30 % of the cases, and when bilateral frequently more marked in one eye. RAUDNITZ has described a similar case in which N was first right-sided, then bilateral, and finally left-sided. Spasmus nutans cannot, however, be considered the cause of N, even though the two symptoms are sometimes coexistent. All authors are of the opinion that N of this type — with or without head nodding — is not at all a serious condition; the prognosis is good and the disorder clears up in a few months. As no ocular or cerebral defect is detectable during the course of the disease, this type of N is interpreted as a physiological disorder (MOORE, MOORAD). Some workers, however, think it possible that infections or other extraneous factors of unknown nature are responsible for its occurrence (ROCHE, HERRMAN).

As to the factors which favour the development of this type of N, it has often been ascribed to the conditions under which the less privileged classes have to live, above all to poor light. RAUDNITZ postulated that the child's eyes suffer if not exposed to sufficient light stimuli at a time when binocular fixation should normally be developing. The child's efforts to fixate lead to erratic movements of the eyeballs. Comparative studies have been made of miner's nystagmus and nystagmus developing in dogs bred in the dark and of ways in which the types of N may be prevented and treated by the provision of better illumination. MOORAD asserts that N arising under these circumstances is in principle of the same nature and should be considered a physiological reaction to living in poor light. However, there are children with unilateral or bilateral N of the so-called physiological type who have lived under privileged conditions with

adequate light (the author's Case I, as well as one of the cases described by Østerberg).

Before dealing with the problem of the pathogenesis of unilateral N, a few words on the pathogenesis of N in general will not be out of place. As is known, the eye is never absolutely still even when fixed. Normally the eye performs nystagmoid movements of minute amplitude during foveal fixation. N may therefore be interpreted simply as an exaggeration of normal fixation movements. The rôle played by binocular vision in the genesis of N is elucidated by some cases described by POSNER, who reported three cases with latent N with an amblyopia of one eye. In these cases the healthy eye became nystagmic when the other eye was covered. In spite of the fact that the visual acuity of the amblyopic eye alone was insignificant (15/200, hand movements, counted fingers at a distance of 1 ft.), it was nevertheless able to counterbalance N and increase the vision of the good eye by 100 % (visus 20/20 right + left; 20/40, 20/50, 20/40 + 2 respectively for the healthy eye). This minimal degree of binocular vision was in other words sufficient to neutralize N. As is known, the functional activity of the CNS is generally such that the cortical centers exercise control over the subcortical. It is known that the extraocular musculature needs a cortical control to render possible the steady uninterrupted fixation which is a prerequisite of good vision. Binocular vision permits a higher order of control by the cortex than does monocular vision and thus plays an essential part in the prevention of N (POSNER). A number of other theories concerning the pathogenesis of N have been put forward, but they do not fit into the picture of so-called physiological nystagmus so well.

The aetiology of *unilateral* N is still very obscure. Many theories have been launched and many different explanations have been suggested. It is generally believed, however, that unilateral N is primarily bilateral, but that the cortical control affects the nuclear regions of the two sides to different degrees and that for some reason or other one side is put out of function. DUANE assumes the presence of an interruption of the intranuclear connections. NEUSTÄTTER theorizes that the movements of the eyes are primarily

independent of one another. A question not discussed hitherto in connection with N is ocular dominance. According to POSNER's elaboration of VERHOEFF's theory of binocular vision (theory of replacement), one eye fixes the object of attention, while the other eye perceives the surrounding field and thus complements binocular vision. If both eyes are of similar visual acuity, these functions may be performed alternately, but in such a manner that one eye is responsible for the fixation during the greater part of the time. From this theory we may possibly reason as follows: as pointed out above, N occurs at a time when the child is training itself for fixation and binocular vision. If in a child only one eye develops the power of fixation — at a stage in the child's life when there is reason to assume that binocular vision has not developed with the high degree of control such vision involves (see above) — one eye will naturally predominate in vision. In the absence of cortical control of the ocular movements, the other will perform exaggerated fixation movements, i.e. physiological N.

Unilateral N of the present type may be confused with those types not infrequently met with in congenital or early acquired amblyopia. The differential diagnosis is then often hard because it is frequently difficult to determine failing vision in children of this age unless it is associated with conspicuous disorders such as albinism and cataract. To exemplify the above a case of toxoplasmosis reported earlier by ENGLESON will be described.

Case II. Two and a half year old girl, squinted from birth. N diag. at nine mos. On admittance to the Paed. Clinic, Lund, examination revealed not only the usual cardinal symptoms of toxoplasmosis (hydrocephalus, intracranial calcification, retinochorioiditis, mental debility, and positive neutralization test), but also left rather coarse N, probably ascribable to her retinochorioiditis, which engaged almost the whole of the macular region of the left eye.

In the following two cases of unilateral N connected with diseases of the CNS will be described.

Case III. Eight mo. old boy whose mother noticed that the left eye had showed a 'vibratory tremor' for five days. Admittance examination showed a normally developed boy with a slight undulating N of the left

eye. Vision apparently good. Normal refraction. Fundi: normal. Neurologically nothing path. Calorie test: normal. After nine days left facial paresis developed and signs of a paresis of the left abducens oculi. Simultaneously the child exhibited changed behaviour, cried violently, etc. L.P.: 12.5 cells (same number of leukocytes and lymphocytes). Nonne-Apelt reaction: neg.; Pandy: slightly pos. Examination of ears showed nothing path. Roentgen examination of processus pyramidalis revealed no signs of apicitis. The patient soon became quieter and the facial paresis disappeared in sixteen days. The N also began to abate, finally disappearing after about two and a half months.

Case IV. Girl 11 mo. old. Heredity: O. Birth weight 2 750 g. Immediately after a rather quick but otherwise normal delivery the patient became generally spastic for thirty min. After a few months the mother thought the child was not like other children. She was quite backward and did not try to grasp things, did not sit up, reacted only weakly to different insults, often cried, and was restless. Mantoux 1 mg: neg. Examination revealed a finely oscillatory right-sided N of undulating type. Fundi: normal. Median: clear. During hospitalization the patient had many attacks of spasm. After ten days sojourn in the hospital she died of bronchopneumonia. Parents would not permit autopsy.

Monocular N has been described in association with a number of diseases of the CNS, especially when located to the cerebellum, cerebellary peduncles, pons, and anterior quadrigeminal bodies, e.g. in congenital lues, encephalitis, sclerosis disseminata, and Friedrich's ataxia (Moorad). To trace the origin of the impulses in Cases III and IV is very difficult because it must be borne in mind that the optic system may be involved by lesions of the most different parts of the CNS, or the optic system may in turn be under the direct influence of the vestibular system. In view of the limited area involved by the symptom, one might in Case III conceivably imagine the disorder to be traceable to the left of the brain stem, in the anterior portion of the fossa rhomboidalis, i.e. in the pons, where the facial and abducens nuclei and the pontine visual center are located. Besides this one might reasonably assume a lesion of the intranuclear connective fibers. On account of the quick regression and the favourable course, the clinical picture coincides best with that of encephalitis. As far as Case IV is concerned, it is impossible to trace the origin of the N because this case exhibited no localizing symptoms. It might possibly

have been a lesion of the nuclei of the eye muscles, or also a disorder of all the paths leading to these nuclei. In this case N must be attributed to a cerebral lesion, possibly an intercerebral haemorrhage that occurred in connection with delivery.

The course and prognosis of N in diseases of the CNS are of course dependent on the nature of the organic changes underlying the disease as such.

Summary

In agreement with earlier opinions, the author considers that unilateral nystagmus may occur in diseases of very different types. A report is given of one case of unilateral nystagmus without any ocular or cerebral defects' being manifest, two cases of unilateral nystagmus in conjunction with diseases of the central nervous system, and one case of unilateral nystagmus in a patient with toxoplasmosis and retinochoroiditis. Various theories concerning the causal factors of nystagmus are discussed.

Résumé

Nystagmus unilatéral dans l'enfance

Conformément aux opinions antérieures, l'auteur constate que le nystagmus unilatéral peut se rencontrer dans des affections de types très différents. On rapport un cas de nystagmus unilatéral sans aucune apparition de trouble oculaire ou cérébral, deux cas de nystagmus unilatéral en connexion avec des affections du systéme nerveux central, et un cas de nystagmus unilatéral chez un patient atteint de toxoplasmose et de rétinochoroïdite. On discute différentes théories sur les causes du nystagmus.

Zusammenfassung

Einseitiger Nystagmus im Säuglingsalter

In Übereinstimmung mit früheren Ansichten meint der Verfasser, dass einseitiger Nystagmus bei Krankheiten verschiedener Art in Erscheinung treten kann. Er berichtet über einen Fall von einseitigem Nystagmus, bei dem sich weder Defekte im Auge noch Hirn zeigten, zwei Fälle von einseitigem Nystagmus mit

gleichzeitigen Erkrankungen des zentralen Nervensystemes und einen Fall von einseitigem Nystagmus bei einem Patienten mit Toxoplasmosis und Retinochoroiditis. Verschiedenen Möglichkeiten werden diskutiert, die als Ursache des Nystagmus bezeichnet werden können.

Sumario

Nistagmus unilateral en la infancia

De acuerdo con las opiniones emitidas anteriormente el autor considera que el nistagmus puede presentarse en varios tipos de enfermedades. Se describe un caso de nistagmus sin otras manifestaciones patologicas oculares o cerebrales, doses casos de nistagmus unilateral asociadas a enfermedades del sistema nervioso central, y un caso de nistagmus unilateral en un enfermo con toxoplasmosis y retinocoroiditis. Se discuten varias teorias concernientes a los factores etiológicos del nistagmus.

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Acute Iron "Poisoning"

by

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At 2: 15 p.m. on Feb. 26, 1948, a two year old girl was admitted to the Banck Hospital, Hälsingborg. She was in a very bad condition, with blood on her face and clothes. She had never been ill, and therefore on the morning of the day of admission her parents had gone away and left her in the care of an old aunt. According to the aunt's report the child began to look ill and vomit at about 1 p.m. The vomitings continued, becoming sanguinolent, and the child's general condition rapidly exacerbated. She came to the hospital barely an hour after the commencement of the illness. She had collapsed and was almost without pulse, perspiring profusely, mentally clouded, and with a temperature of 35.8° C. The heart sounds were dull but the rhythm regular. The abdomen was meteoristic, not soft, but without perceptible tenderness. The liver and spleen were not palpable. She had no swollen lymph glands. The pharynx contained blood but did not otherwise present anything particular. On account of the patient's general condition and the uncertainty concerning its issue she was given a blood transfusion. The blood tests performed a little later disclosed 5 mill. erythrocytes and 79 000 leukocytes with 69 per cent neutrophils without pathological forms. She had 216 000 thrombocytes and a prothrombin of 75. After the child's general condition had improved, her temperature rose to 38.5° C. On account of this rise in temperature, the white blood picture, and the incomplete anamnesis, she received penicillin in large doses. There seemed to be a possibility of an acute infection suggestive of sepsis, perhaps phlegmonous gastritis. The patient received bits of ice,

lemon juice, and, gradually, some liquid food. She continued to vomit during the subsequent days, while the Weber test of both the vomit cast up from the stomach and the stools, which had contained blood on admission also, rapidly became negative. During those first days there were rises in temperature of up to 38.8° C.

On the day after the commencement of the illness the child's mother discovered that her box of »ferrofer forte» tablets was empty. Such tablets contain 0.267 g of $FeCl_2 = 75$ mg of Fe^{++} each. The mother thought that there had been about twenty tablets left in the box, and her four year old son declared that his little sister had eaten them the preceding morning. Consequently it was possible to reconstruct what had happened on the day of the onset of the illness. The child had breakfasted on gruel and some bread and butter at 7: 30 a.m. At about 10 o'clock, when she was left alone for a short time, she very likely swallowed the tablets, probably on a nearly empty stomach. The question immediately arose whether this might have been the cause of the child's symptoms, even though in a pharmacological textbook, $FeCl_2$ was reported to have no caustic effect and it was stated that overdosage involved no risk. It is known that perorally applied iron preparations may give rise in certain individuals to dyspeptic symptoms, vomitings, obstipation, or diarrhoea. Moreover, a single Blaud pill may sometimes cause gastric disturbances. The disturbances are more common after ferric than after ferrous salts (GOODMAN & GILMAN). It is known that this iron effect is due to the fact that heavy metals even in weak solutions have an astringent influence on the mucous membrane — in stronger solutions the influence is more destructive, with necrosis of superficial epithelial layers or of the entire mucosa. This local effect is due to the power which heavy metals have even in very weak solutions of precipitating the albumin substances and forming a composition the nature of which is not yet known. Acids are thereby set free, and the local effect is a combination of metal and acid influence. Whether the result is an astringent or a more irritating effect cannot be predicted immediately, because a number of different factors play a part.

Metals of different gravity have different effects, and in this connection it may be mentioned that iron has the strongest effect immediately after lead (EDMUNDS and GUNN). Different salts of the same metal do not have equally marked effects. The more complete the dissociation in ions is, the more rapidly does the reaction with the proteins take place and the more intense does the effect become. Therefore the more ionized inorganic salts produce a stronger effect than do the slowly dissociating organic compounds. The salts with the strongest caustic action of any metal whatever are thus the chlorides and the nitrates, provided that they are soluble. The sulfates should be much less irritating, whereas the salts with the weakest local action are the organic lactate, acetate, citrate, and tartrate. However, other factors also enter into the degree of irritation, such as the condition of the mucosa and the amount of protein with which the iron salts come in contact before they reach the live tissues.

As was mentioned before, dyspeptic symptoms are more pronounced after ferric salts than after ferrous salts. This is quite in accordance with the circumstance that ferric salts have a more astringent and irritating influence than the corresponding ferrous salts. Presumably, however, the ferrous salts have an astringent effect. Thus the possibility is implied of the appearance of a (possibly) reversible iron albumin combination in the most superficial epithelial layer with formation of a membraneous protection against further chemical or mechanical irritation. But of course there can only be a difference of degree between an astringent effect and a more profoundly irritating — caustic — necrosing influence with ulcerations and haemorrhages. Thus it is warrantable to imagine that a sufficiently large single dose of $FeCl_2$ introduced into the fasting stomach of a little child might entail serious consequences. If the pharmacological textbook alleges, as was mentioned before, that $FeCl_2$ has no caustic action, it is presumably assumed that the dosage has been calculated *lege artis*. The assertion in the textbook that overdosage involves no risk is probably based on the circumstance that no case of acute ferrochloride injury has heretofore been observed.

However, in 1947 SOMERS examined by means of animal ex-

periments the effect of very large peroral doses of the iron preparations most frequently encountered in England, namely, ferrous sulfate, ferrous carbonate, ferrous gluconate, ferric chloride, iron and ammonium citrate. He summarized his experiences to the effect that certain soluble iron salts, whether ferrous or ferric compounds, organic or inorganic acids, normally ionisable or complex, were toxic in very large doses for at least some laboratory animals, leading to necrosis of the mucous membrane of the stomach and a certain fatty degeneration and necrosis of the lobuli hepatis. SOMERS is of the opinion that this uniform effect of the different iron preparations is due to the circumstance that after having been dissolved in the stomach they are all reduced to ferrous salts, which are thus held entirely responsible for any injuries which may occur.

On examining the literature it becomes evident that cases of iron »poisoning» are extremely rare. Thus MCGUIGAN (1926) observed the case of a man who died after having taken 45 ml of iron tincture. SMITH and COOK (1934) reported the case of a girl who swallowed 28 g of $FeSO_4$, but recovered. FORBES (1941) has published two cases of ferrous sulfate »poisoning» with lethal issue after collapse and bloody vomit in two boys aged one and three years. They had swallowed respectively 25 and 45 tablets of 0.2 g each, i.e. about 1 500 and 3 000 mg of Fe^{++} respectively. THOMSON (1947) has likewise published two cases of ferrous sulfate poisoning in infants, one of whom, a sixteen month old girl, died after having swallowed about 25 tablets. According to a personal communication from Dr. Henning Magnusson, Physician in Chief at the Sachs Children's Hospital, Stockholm, a case of very severe ferrochloride poisoning with extensive necroses through all the layers of the wall of the stomach after ingestion of about 40 tablets of ferrofer forte has been treated in his hospital. That case will be published elsewhere.

The iron being resorbed to a very slight degree, the symptom picture will be entirely dominated by the local irritation or possibly corrosion. The subsequent influence on the general condition is probably due essentially to local action on the digestive apparatus, even though signs of a general toxic lesion have been

observed. The postmortem examination of FORBES' second case disclosed in addition to an oedematous, necrotic, bleeding stomach mucosa degenerative cell lesions in the parenchymatous organ too, particularly in the liver. That this is not the rule is revealed by the autopsy of the case observed by THOMSON, i.e. the sixteen month old girl, all of whose parenchymatous organs were found to be intact.

Experimental examinations of animals following administration of very large doses have been performed particularly by SOMERS (as mentioned before) and by FORBES (1947). Experimenting with ferrous sulfate on cats and guinea pigs, the latter was able not only to demonstrate a purely local caustic effect on the mucous membrane of the stomach, but also (like SOMERS) a general toxic lesion with degenerative changes amounting to complete necrosis of the liver cells and a cloudy swelling of the renal tubuli.

There is good accord between the clinical symptoms in the previously reported cases and the case observed in the Banck Hospital. All were characterized by poor general condition, a low temperature, bloody vomit, and bloody stools. Necrosis of the ventricle mucosa of the girl treated in the Banck Hospital appeared on roentgenograms taken for the first time twelve days after her admission to the hospital. In this case a deep ulcer niche was seen on the inside of a ventricle which was displaced in the canal region and had fixed contours. The roentgen examination repeated a month after the patient's admission disclosed a picture which, according to the roentgen-diagnostic department in Lund, was suggestive of corrosion in the stomach mucosa. Subsequently the roentgenological changes decreased and at a re-examination performed on September 14, 1948, only a slight constriction was left beneath the fundus. Otherwise the stomach showed nothing abnormal.

The patient's general condition continued poorly for a long time; she looked ill and tired, and was very pale, with dark rings round her eyes. Her temperature was subfebrile for about six weeks, but the white blood picture had returned to normal after about a fortnight. On discharge from the hospital on May 14,

when she seemed to have recovered entirely, an examination of the gastric juice disclosed a histamine-refractory achylia which still persisted when she was re-examined on Sept. 16, 1948.

Ferrous sulfate tablets are evidently an iron preparation prescribed very frequently in England. Previously it has been regarded as quite harmless. Ferrochloride has also had an excellent reputation, in some quarters being regarded as the »physiological» iron preparation. It is evident, however, that precaution is necessary even with these preparations; in the hands of children and in sufficiently large quantities the consequences may be fatal.

Summary

Ferrochloride, which has been considered a completely harmless iron preparation, may, like large doses of ferrous sulfate, prove very dangerous, at any rate to children. On several occasions there have been references in English literature to »poisoning» with the latter. A case is reported here of ferrochloride poisoning in a two and a half year old girl who took a single dose of c. 1 500 mg $FeCl_2$ with resultant necrosis of the mucous membrane of the stomach, haematemesis, blood in the stools, and a condition of collapse. — Even more innocuous medicines should be kept out of the reach of children.

Résumé

Intoxication aiguë par le fer

Le ferrochlorure, qui a été considéré comme une préparation ferreuse absolument sans danger, peut, comme les fortes doses de sulfate ferreux, se révéler très dangereux, en tout cas pour les enfants. A plusieurs occasions, dans les écrits anglais on a fait mentions d'empoisonnement (poisoning) dû à ces derniers. On signale ici un cas d'intoxication par le ferrochlorure chez une fillette de deux ans et demi, qui prit une seule dose d'environ 1 500 mg de $FeCl_2$, et qui présenta une nécrose de la muqueuse gastrique, une hématémèse, des selles sanglantes, et un état d'asthénie.

Des médicaments même plus inoffensifs encore devraient être gardés hors de portée des enfants.

Zusammenfassung

Akute Vergiftung mit Eisenpräparate

Man betrachtete bisher das Ferrochloridpräparat wie auch Ferrosulfate als vollkommen harmlos. Es stellte sich aber heraus, dass grössere Dosen für die Kinder sehr gefährlich sein können. Zu wiederholten Malen sind in englischen Zeitschriften Mitteilungen über Vergiftungen nach Gebrauch von grossen Dosen dieser Eisenpräparate erschienen.

Es wird berichtet über ein Mädchen von $2\,^1/_2$ Jahren. Nach Einnehmen von 1 500 mg $FeCl_2$ in Einzeldosis folgte Necrose der Magenschleimhaut, Haematemesis, Blut im Stuhl und Kollapszustand. Medikamente sollten nicht in die Hände von Kindern gelangen.

Sumario

Intoxicación aguda por el hierro

El cloruro de hierro ha sido considerado como un preparado completamente inocuo, pero puede de la misma manera que el sulfato ferroso, resultar muy peligroso en los niños. En varias oportunidades han aparecido referencias en la literatura inglesia, sobre intoxicaciones con este ultimo preparado. Se refiere aqui, a un caso de intoxicación por el cloruro de hierro en una niña de dos años y medio que ingirio una sola dosis de 1 500 mg de cloruro de hierro, resultando de ello una necrosis de la mucosa estomacal, con hematemesis y melena, aconpañado de un estado de colapso. Los medicamentos por mas inocuos deben de mantenerse fuera del alcanze de los niños.

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Some Observations on Erythema Nodosum

by

RUSTIN MCINTOSH

When a disease or a syndrome displays different characteristics in one part of the world from those found elsewhere, a study of these differences may lead to a better understanding of its underlying mechanisms.

The relative frequence of occurrence of erythema nodosum (er. n.) in the Scandinavian countries (5, 6, 8, 10, 12, 13, 15, 17, 19, 20, 24, 25), and especially in Sweden, has often provoked comment. Observers in other geographical areas may have believed for a time that the syndrome itself, as observed in Scandinavia, was peculiar to the North, or that they themselves could have been lacking in diagnostic perception. For many years, however, it has been clear beyond question that the syndrome is the same wherever it is found, and that the differences in its incidence are real and not mere accidents of observation. The strong preponderance, in Scandinavia, of cases of er. n. occurring in association with primary tuberculosis has been matched by similar experiences in France (4) and to some extent elsewhere (9, 18), but not in the United States (2, 14, 21). In addition, the wide variety of infections with which er. n. may be associated in some apparently causal relationship (beta-haemolytic streptococcus (2, 3, 13, 21), alpha-haemolytic streptococcus (7), lymphogranuloma venereum (10), trichophytosis (1), coccidioidomycosis (23)) has received perhaps more emphasis in other parts of the world than in Scandinavia. The precise interpretation of instances of er. n. which accompany treatment with sulfathiazole and some of the other sulfonamide drugs remains to a considerable degree indeterminate.

In the course of 16 years er. n. has been observed in 43 patients admitted to Babies Hospital in New York, a case frequency of approximately 1 in 1 200 admissions. Children of every age up to 13 years are received in the hospital, so that childhood experience as well as that of infancy has been fairly represented. The ages of more than half of the patients fell into a narrow prepubertal zone, 7 to 10 years; 3 cases were seen in infants 1 ½ to 2 years of age. Boys and girls were about equally affected. A smoothed curve of seasonal incidence shows a peak in February, a nadir in July and August. One patient had suffered 3 previous attacks, 1 had had 2, and in 3 instances the observed attack was the patient's second; in all the rest the attack observed was the initial one. A family history of allergic disease (infantile eczema, food urticaria or angioneurotic oedema, hay fever, or asthma) was obtained in 17 % of the cases in which this information was specifically recorded — an incidence not significantly higher than that which is found in a random sample of the hospital's population. A previous history of allergic disease in the patient himself was rarely elicited. In about half the cases an attack of »sore throat» had been complained of prior to the onset of the eruption. Other preceding diseases or premonitory complaints were of such diverse nature that little importance could be attached to them in the search for underlying mechanism of pathogenesis. Sulfonamides had been administered to not more than half a dozen of the patients in the series prior to the outbreak of nodules.

The associated diseases which could be clearly identified were surprisingly few in number. In only 4 cases could primary tuberculous infection be established with reasonable certainty, though the number of reactors to tuberculin greatly exceeded this figure and in several of them the possibility could not be excluded that the infection was in its initial stage. One indisputable example of rheumatic fever was encountered, and two questionable cases. Many patients exhibited skin sensitivity to beta-haemolytic streptococcal test material, and also an accelerated E.S.R., without manifesting any of the clinical phenomena of rheumatic fever. On the whole, it must be admitted that the search for associated

disease has in our experience justified no conclusion as to any specific aetiology of er. n. Quite the contrary, we have like others been led more and more to explore the circumstances of a patient's skin sensitivity to bacterial or other specific proteins when er. n. is present.

The point of view just expressed has not prevailed throughout the full 16 year period covered by this study. Some of our records contain no observations of skin tests of any sort; others have only meager data. The majority of patients whose er. n. was associated with sulfonamide treatment were studied in other ways, especially by direct search for pathogenic organisms. In a few instances skin tests with the sulfonamide in therapeutic use were made, by intracutaneous injection of the drug either alone or in combination with human plasma — with negative results in every case.

Table 1 shows the results of skin tests made with bacterial antigens. Its many lacunae reflect a changing type of enquiry into the pathogenesis of er. n. over the years. Even with the incomplete data presented, however, certain inferences may be drawn.

1) Among the total number of cases of er. n. seen in a New York paediatric service, those associated with tuberculosis are in the minority. This point has already been made by LINCOLN, ALTERMAN, and BAKST (14).

2) Among the cases with marked sensitivity to beta-haemolytic streptococcus (and only the severe dermal reactions were interpreted as significant), the majority fail to show clinical signs of rheumatic fever at any time, either during the course of er. n., prior to its onset, or subsequently.

3) A patient who has had er. n. associated with primary tuberculosis may have a second attack of er. n. associated with a high degree of skin sensitivity to beta-haemolytic streptococcus.

4) In our series every second or subsequent attack of er. n. was associated with a strongly positive streptococcal test. Some of the patients with multiple attacks of er. n. had positive tuberculin tests, but not all.

Table 1

Skin sensitiveness to various antigens in erythema nodosum.

(Key: + = strongly positive test. — = absent or weak reaction. 0 = test not made.)

	Number of Patients	Tuberculin	B-haemolytic Streptococcus	Coccidioidin	H. Influenzae Staph. Haemolyt. M. Catarrhalis D. Pneumoniae (each separately)
	5	+	—	0	0
	18	—	+	0	0
	2	—	+	0	—
	1	—	+	—	0
	6	+	+	0	0
	3	—	0	0	0
	1	—	0	—	0
	1	+	0	0	0
Number of Positive Reactors		12	27	0	0
Total Number Tested	37	37	32	2	2

5) When a patient with er. n. fails to react strongly to intracutaneous injection of the two antigens most frequently concerned, tuberculin or beta-haemolytic streptococcal substance, further search for specific sensitivity is called for. The antigens selected will doubtless be determined in part by the accompanying clinical picture (e.g., Frei antigen, trichophytin, alpha-haemolytic streptococcus) or by special epidemiological circumstances (e.g., coccidioidin).

Can a high degree of antigen-specific skin sensitivity satisfactorily account, then, for all cases of er. n.? With the exception of the sulfonamide cases, which fail to show a positive skin test with any sulfonamide antigen that has thus far been tested, an affirmative answer would seem to apply to any experience in which an adequate variety of antigens has been employed. Will this explanation, in turn, embrace all other aspects of the

er. n. problem? Consideration of this question brings us back to the peculiar concentration of case material in Scandinavia.

One explanation that has been offered (26) for geographical localization ascribes to Swedish racial stock an inordinate frequency of allergic manifestations of all kinds. If this is true, the susceptibility of the Swedish people to er. n. may occasion no surprise.

There are, however, two items of evidence on the other side. The first involves a calculation of probabilities. Accurate morbidity figures in regard to allergic diseases are notoriously difficult to assemble. Making every allowance, however, for differences in interpretation of what actually constitute allergic stigmata, it is unlikely that the ratio of allergic morbidity in the Swedish population at large to that of a mixed American population such as that of New York City children is greater than 3 : 2 or, at the most, 2 : 1. Is this order of difference consonant with the recorded difference in morbidity of er. n., which has a ratio approaching 50 : 1 when the experience of the Gothenburg Hospital is compared with that of either of two New York paediatric services?

The second fragment of evidence has to do with the experience of Americans of Swedish stock. If susceptibility to er. n. represents a genetic trait, then it can be expected to survive migration and should affect the frequency with which er. n. appears in the areas where large numbers of people of Swedish ancestry have settled. Here again, accurate data are not to be had; yet the impression of a proved student of the er. n. problem deserves to be quoted. Spink, who had reported in 1937 the case material of the Boston City Hospital covering an 11 year period, moved to Minneapolis in that year and has been since then continuously on the staff of the University of Minnesota Hospital. He reports (22) that the incidence of er. n. appears to be no greater in that area of strong Swedish penetration than it was in Boston. McQuarrie (16) likewise finds the case frequency of er. n. in the paediatric service of the Minnesota University Hospital no different from that observed in other cities of this country.

A shadow of doubt is thus cast on the hypothesis that the

genetic constitution of the host materially influences the incidence of er. n. Without in any degree minimizing the part which allergy plays in its pathogenesis, one must admit that certain of its attributes still require further elucidation.

Summary

Erythema nodosum is seen less frequently in the United States than in the countries of Scandinavia. In 16 years 43 cases have been observed in children less than 13 years of age in the Babies Hospital of New York, an incidence of about 1 case in 1 200 admissions. The majority of patients tested showed skin sensitivity to beta-haemolytic streptococcus, although only a small fraction of them were actually rheumatic or subsequently developed rheumatic fever; a minority of the total group had positive tuberculin tests. On the basis of a limited experience the hypothesis is advanced that erythema nodosum, when it is causally related to tuberculosis, is associated with the efflorescence of the primary infection, and that cases which appear months after the initial tuberculous infection, or second attacks developing in tuberculin-positive children, represent the expression of hypersensitivity to some other allergen, often a beta-haemolytic streptococcus. In any given case of erythema nodosum, before one accepts the relationship of the eruption to tuberculosis on the basis of a positive tuberculin test alone, it is desirable that a search be made for hypersensitivity to other antigens.

The frequency of occurrence of erythema nodosum among inhabitants of the Scandinavian countries does not lead to its more frequent appearance in American descendants of Scandinavian stock, as one might expect if susceptibility were genetically transmitted as a constitutional trait.

Résumé

Quelques observations sur l'érythème noueux

Il y a moins de cas d'érythème noueux aux Etats Unis que dans les pays scandinaves. En 16 ans on a observé 43 cas chez les enfants de moins de 13 ans admis au Babies Hospital de New-York, soit une proportion de 1 cas pour 1 200 admissions.

Les examens, recherches et analyses faites sur le plus grand nombre des patients montrèrent une sensibilité cutanée au streptocoque bêta hémolytique, quoique seulement une petite fraction des cas fit réellement son apparition au cours ou au décours d'une fièvre rhumatismale. Un petit nombre de patients présentait une intradermo réaction à la tuberculine positive. Sur la base d'un matériel restreint, on émet l'hypothèse que l'érythème noueux, quand il est en rapport avec la tuberculose, est associé à l'éclosion d'une primo infection, et que les cas qui apparaissent plusieurs mois après l'infection initiale ainsi qu'une deuxième poussée survenant chez les enfants à réaction tuberculinique positive, sont l'expression d'une hypersensibilité à quelque autre allergène, souvent un streptocoque beta-hémolitique.

Dans tout cas d'érythème noueux, avant d'admettre la parenté de l'éruption avec la tuberculose sur la seule base d'un épreuve tuberculinique positive, il sera bon de rechercher la sensibilité à d'autres antigènes. Le fait que l'on trouve de nombreux cas d'érythème noueux parmi les habitants des pays scandinaves n'implique pas une fréquence plus grande chez les américains descendants de souche scandinave, comme on pourrait s'y attendre si la susceptibilité à l'érythème noueux était génétiquement transmise comme un trait constitutionnel.

Zusammenfassung

Einige Beobachtungen über Erythema Nodosum

Erythema Nodosum kommt viel seltener in den Vereinigten Staaten als in den skandinavischen Ländern vor. In einem Zeitraum von 16 Jahren wurden 43 Fälle bei Kindern unter 13 Jahre im Kinderspital von New York beobachtet, ein Fall im Durchschnitt von 1 200 Aufnahmen. Die Mehrzahl der untersuchten Patienten zeigte für beta-hämolytische Streptokokken Hautempfindlichkeit, obwohl nur ein kleiner Bruchteil unter ihnen wirklich rheumatisch war oder in der Folge rheumatisches Fieber entwickelte. Eine Minorität in der ganzen Gruppe zeigte positive Tuberkulinprobe. Auf Grund begrenzter Erfahrungen wird die Hypothese aufgestellt, dass Erythema Nodosum, wenn gelegentlich in Verbindung mit Tuberkulose, in Zusammenhang mit dem

Aufscheinen einer vorhergehenden Infektion steht, und dass Fälle, welche Monate nach der ersten Infektion mit Tuberkulose in Erscheinung treten, oder auch wiederholte Anfälle sich bei positiven Tuberkulinkindern entwickeln, eine Hypersensitivität für irgendein anderes Allergen, oft beta-hämolytischen Streptokokken bedeuten. Bei jedem gegebenen Fall von Erythema Nodosum ist es wünschenswert, dass, ehe man Ausschlag mit Tuberkulose nur auf Basis einer positiven Tuberkulinprobe in Verbindung bringt, genau untersucht, ob eine Hypersensibilität gegen andere Antigene vorliegt. Die Häufigkeit des Auftretens des Erythema Nodosum bei den Bewohnern der skandinavischen Länder führt jedoch nicht zu einer häufigeren Erscheinung bei den amerikanischen Nachkommen skandinavischer Einwanderer, wie man erwarten könnte, wenn Empfänglichkeit als konstitutioneller Zug genetisch übertragbar wäre.

Sumario

Algunas observaciones sobre eritema nudoso

El eritema nudoso se ve menos frecuentemente en los Estados Unidos que en los paises Escandinavos.

En el curso de 16 años se observaron 43 casos en el Hospital de niños de New York en niños menores de 13 años, es decir una incidencia que corresponde aproximadamente a un caso por cada 1 200 admisiones. La mayoria de los enfermos examinados presentaron una sensibilidad cutanea al estreptococo beta-hemolitico, a pesar de lo cual solamente una pequeña fracción de ellos eran reumaticos o desarrollaron posteriormente fiebre reumatica. Una minoria del grupo total, presentaron una reacción tuberculinica positiva.

Basandose en una experiencia limitada, se adelanta la hipótesis, de que el eritema nudoso cuando aparece casualmente relacionado a la tuberculosis, se encuentra asociado a la eflorecencia de la infección primaria, y que en los casos en que aparece meses despues de la tuberculosis inicial, o en los ataques secundarios que aparecen en niños con una reacción tuberculinica positiva, representa la expresión de una hipersensibilidad a algun otro alergeno, frecuentemente el estreptococo beta-hemolitico. En

cualquier caso de eritema nudoso, antes de aceptar la relación de la erupción a una tuberculosis, basandose solamente en una reacción tuberculinica positiva, es deseable que se efectúe una investigación de sensibilidad frente a otros antigenos. La frecuencia de la incidencia del eritema nudoso entre los habitantes de los paises Escandinavos, no lleva a una mayor frecuencia en los Americanos decendientes de Escandinavos, como seria de esperar, si la susceptibilidad fuese geneticamente transmitida como un caracter constitucional.

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FROM THE SACHS CHILDREN'S HOSPITAL AND THE INSTITUTE OF HYGIENE OF KAROLINSKA INSTITUTET, STOCKHOLM.

Coli-Meningitis in a Newborn Infant

Report of a Case Treated With Streptomycin and a Study of the Formation of Antibodies

by

J. HENNING MAGNUSSON, GUNNAR GILLE, and GUNNAR LAURELL

The problem of coli-meningitis in newborn infants has long aroused great interest. FOTHERGILL and SWEET; CRAIG, BARRET, AND ASSOCIATES; and FLENSBORG have reviewed the literature on the subject in their publications and collected the reports of cases published hitherto.

Meningitis in newborns caused by coli bacteria is not a common disease, although the statements regarding its frequency vary considerably. CRUICKSHANK found thirty three cases of meningitis, i.e. 4 %, in eight hundred postmortems on newborns. A bacteriological examination (culture or direct preparation) was made in twenty three cases. In the twenty one in which cultures were made, eleven showed growths of coliform bacteria, seven of haemolytic streptococci, and three of pneumococci. CRUICKSHANK nevertheless quite correctly doubts the pathogenic importance of coli bacteria in several of the cases. FOTHERGILL and SWEET's material included twenty nine clinical cases of meningitis in newborns. Eight of them suffered from coli-meningitis and were aged one—five weeks. The writers found that haemolytic streptococci and pneumococci together were more a common cause of meningitis during the first four weeks of life than coli bacteria. CRAIG's series consisted of twenty one newborns with meningitis, 71 % of whom were prematures. The distribution of the material was as follows: ten cases caused by coli bacteria, five by Staph. aureus, four by haemolytic streptococci, one by the Salmonella group of bacteria, and one by pneumococci.

The pathogenesis of meningitis in newborns has been discussed by several writers and particularly thoroughly by CRAIG. He listed a large number of theoretically possible portals of entry and attached particular importance to lesions of the skin and mucosa. Such lesions were present in no less than fifteen of his twenty one cases. In the majority of them concurrent septicaemia was also demonstrated.

Symptomatologically, coli-meningitis in newborns does not differ from meningitis of other origin. As in the other forms, the classical signs of meningitis are often lacking at this age.

In all the cases mentioned in the foregoing, the diagnosis was made on the basis of culture of the cerebrospinal fluid and direct preparations thereof. Usually a serological diagnosis was not made. An exception is one case reported by BARRET AND ASSOCIATES in which a determination of the antibodies was made once. This was a boy aged two weeks. Coli bacteria were cultured from the blood and the cerebrospinal fluid but no antibodies against the bacteria could be demonstrated in the serum of the patient.

In the material from the literature in which chemotherapy was not used, the mortality rate was found to be approximately 80 % (1). Where the patients recovered, various kinds of residual conditions are described, most commonly hydrocephalus (1) but also amaurosis (6). The number of cases treated with sulfonamides is not sufficiently large to permit an estimation of the value of such therapy.

An account will now be given of the case observed by us.

Clinical Observations

The infant, a girl, was born April 19, 1948, and weighed 3 655 g at birth. The mother (ABBH 1468/48), a forty three year old octipara, was admitted to the maternity department after a normal pregnancy during which there was no proteinuria, anaemia, or infection other than mild bronchitis. Labour lasted for twenty four hours and the child was born with the umbilical cord wound once around the neck. There were no complications during the puerperium and the mother was discharged from hospital on

the eighth day after parturition. It was noticed as early as at birth that the right corner of the child's mouth was drawn downwards when she cried, while the left corner was immobile. She appeared normal in other respects during the first days. On the fourth day (22/4) her temperature rose to 39.1° C, she became cyanotic, and her respiration was laboured. Stimulation was given in the form of »tonocard» and oxygen and she was remitted the same day to the Sachs Children's Hospital (Journal No. 361/48).

Condition on Admission, April 22, 1948. Temperature 38.2° C. The visible symptoms were an excessive traction of the mouth to the right when crying, an isolated cutaneous inflammation about 2 cm in diameter on the anterior aspect of the left upper arm, and a few smaller similar foci on other parts of the body. The liver and spleen were not palpable. Leukocytosis: 10 250 white cells per ml. ESR normal. A few granular cylinders were found in the urinary sediment but otherwise nothing abnormal.

The patient was given breast milk, later supplemented by protein hydrolysate in the form of Aminosol. Sulfonamide (2-sulfonamido-4-methyl-pyramidine) and penicillin therapy was started immediately.

The temperature fell rapidly and during the next three days the patient was afebrile and her general condition was entirely unaffected. The cutaneous inflammation disappeared after about twenty four hours, with the exception of the area on the left arm. After about two days it developed into a reddish-blue infiltration which gradually spread to the lower part of the upper arm and the upper part of the forearm. On the eighth day of life the temperature began once more to rise and the following day the infiltration on the arm showed signs of resolution. After incision plentiful grey mucous pus was evacuated. Culture showed a growth of Escherichia coli. The strain was streptomycin-sensitive but sulfa- and penicillin-resistant.

As soon as the investigations were complete, i.e. on the fifteenth day of life, penicillin therapy was replaced by streptomycin, 2.5 cg × 8 intramuscularly. The abscess on the left arm

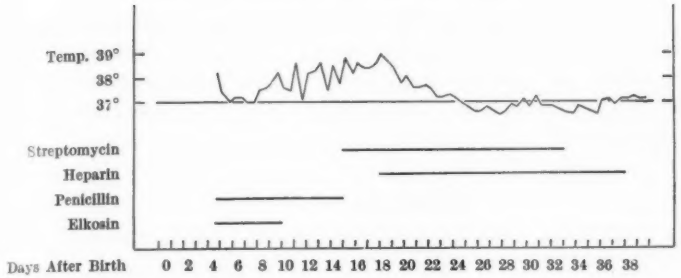

Fig. 1. Survey of the temperature and therapy.

healed rapidly with this treatment but the temperature remained at a level of approximately 38.5° C for the following three days. The general condition of the patient began to be somewhat affected and she lost weight. Since the cerebrospinal fluid from a lumbar puncture gave the same result on culture as the pus from the abscess on the left arm, it was possible to make the diagnosis of coli-septicaemia and meningitis. Intramuscular streptomycin therapy was continued and on each of the lumbar punctures made at the ages of nineteen, twenty three, and thirty days, 5 cg of streptomycin was also given intrathecally. In connection with these injections, the infant was consistently generally affected for approximately forty five minutes, with shallow irregular respiration and cyanosis. In order to counteract the precipitation of fibrin in the meninges, heparin was also given in intramuscular doses of $0.20 + 0.15 + 0.15 + 0.20$ ml daily.

After ten days' streptomycin therapy, the patient became afebrile, her general condition became normal, and she began to gain weight. At the same time the cerebrospinal fluid became sterile. When she had been afebrile for ten days and two successive lumbar punctures had shown sterile cerebrospinal fluid, the therapy was stopped. Rapid improvement continued and the infant increased 500 g in weight during the last two weeks in hospital. She was discharged on June 4, just over six weeks old. She was then in very good condition and a slight facial paresis on the left side — which could not be attributed to the coli bacteria infection — was the only remaining clinical symptom.

Control examinations were made a little more than three weeks and four and a half months, respectively, after discharge from hospital. The general condition of the patient was excellent on both occasions and no residual symptoms of the coli bacteria infection could be found.

Bacteriological Findings

A gram-negative bacteria was isolated from the cerebrospinal fluid and from the incised abscess on repeated occasions during the acute stage of the illness. As regards its morphology and properties in the culture, it was a coliform bacteria with the following biochemical reactions (Table 1).

Table 1

Biochemical properties of test strains.

Strain	Indole	Methyl Red	V.-P.	Citrate	Liquefaction of Gelatine	H_2S
14 445	+	+	−	−	−	−
6 158	+	+	−	−	−	−

14 445 isolated from abscess. 6 158 isolated from cerebrospinal fluid.

According to this table the strains tested belong to the Escherichia coli group of coliform bacteria. Nevertheless, during recent years several writers have pointed out the relative values of the biochemical reactions and the indefinite borderlines between the various groups in the coliform organisms. The ability of the isolated strains to ferment the most usual kinds of sugars was also tested. Rhamnose, lactose, dulcitol, mannitol, and salicin were fermented with the formation of acid and gas, whereas saccharose and adonite were unaffected.

Serology

The strains isolated from both the cerebrospinal fluid and from the abscess were tested against the patient's own serum by means of an agglutination reaction. The method used for the

treatment of the antigen for the reaction was that elaborated by KAUFFMANN and VAHLNE. A sample of serum was taken from the patient on the twelfth and eighteenth days of the illness. Both these sera agglutinated the strains found in dilutions between 1/5 120 and 1/10 240. It was demonstrated that both strains were identical by means of cross-agglutination after absorption. In a test against the O-groups in VAHLNE's classification, an agglutination was obtained for Group 14, but the titer was too low to be considered specific. The strains were thus not identical with earlier tested coli strains as regards the antigen structure. About ten different strains of coli were isolated from the patient's throat and from the mother's faeces. None of these, however, was identical with the pathogenic strains.

Discussion

The bacteriological investigation showed that the bacteria found belonged to the coliform bacteria, presumably to the Escherichia coli group. Meningitis in newborn infants caused by coli bacteria is not a common disease. A serological test has been made in only one previous case and the result was then negative. In the case described here, high agglutination titers against the strains demonstrated were obtained with serum from the patient. These high titers strongly support the assumption that coli bacteria caused meningitis in this case. It was also possible to show by means of cross-absorption that both the strains isolated were identical. The abscess that occurred in the course of the disease was thus caused by the same bacteria that gave rise to meningitis. It is probable, under such conditions, that septicaemia was present. In cases described earlier the mortality rate was high and no effective therapy had been found. The strains in question in our case were resistant to penicillin and sulfa drugs but sensitive to streptomycin. Streptomycin therapy proved to be effective and the patient was entirely healthy when discharged from hospital.

Summary

A report is given of a case of acute meningitis and an abscess in the left upper arm caused in a newborn girl by coli bacteria.

Table 2

Examinations of cerebrospinal fluid.

Age	Appearance of Fluid	No. of Cells per mm³				Fluid Sugar mg%	Blood Sugar mg%	Protein		Culture of Fluid	Remarks
		Leuko-cytes	Poly-morphs	Mono-nuclears	Erythro-cytes			Pandy	Nonne		
5 days	Bloody	6 910	—	—	10 900	—	—	+ + +	+ + +	—	Leukocytes partially destroyed
15 days	Yellow, turbid	8 000	—	—	210	21	65	+ + +	+ + +	Plentiful growth of Escherichia coli	No increased pressure. Leukocytes partially destroyed and difficult to assess.
19 days	Yellow, clear	340	203	137	67	—	—	+	+	Growth of Escherichia coli	No increased pressure. Microscopical examination: some coli bacteria.
23 days	Pale yellow, clear	148	65	83	11 300	—	—	+	+	No growth	
30 days	Pale yellow, clear	54	31	23	37	56	110	+ +	+	No growth	Pressure normal
40 days	Practically colourless, clear	29	4	25	—	49	85	+	+	No growth	

The antibody formation was studied. The infant was treated successfully with streptomycin.

Résumé

Coli-méningite chez un nouveau-né

Rapport est fait d'un cas de méningite aiguë et d'un abcès du bras gauche, causés par le colibacille chez un nouveau-né de sexe féminin. La formation d'anticorps fut étudiée. L'enfant fut traitée avec succès par la streptomycine.

Zusammenfassung

Coli-Meningitis bei einem neugeborenen Kind

Ein Bericht liegt vor über einen Fall akuter Meningitis und einem Abszess am linken Oberarm, verursacht durch den Bacillus coli bei einem neugeborenen Mädchen. Die Bildung von Antikörpern wurde untersucht. Das Kind wurde erfolgreich mit Streptomycin behandelt.

Sumario

Meningitis a coli en un recién nacido

Se describe un caso de meningitis aguda con un absceso en el brazo izquierdo en una niña recién nacida, producido por el bacilo Coli. Se estudio la formación de anticuerpos. El niño fue tratado con estreptomicina con buenos resultados.

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FROM THE SAMARITEN CHILDREN'S HOSPITAL, STOCKHOLM.

Hypertrophic Pyloric Stenosis — A Survey of 136 Successive Cases — With Special Reference to Treatment With Scopyl

by

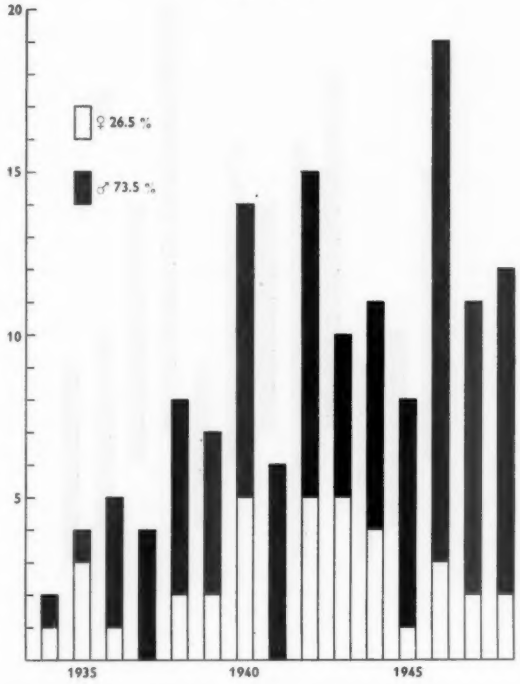
NILS MALMBERG

During the period 1934—1948, one hundred and thirty six cases of so-called hypertrophic pyloric stenosis were treated at the Samariten Children's Hospital, Stockholm. This paper presents a report on these cases with some reflections on the nature of the disease to which a study of this series gave rise.

In spite of intensive research, the pathogenesis of the disease in question must still be regarded as obscure. First with regard to nomenclature, the term »pyloric stenosis» is misleading. »Stenosis of the canalis egestorius» would be more appropriate, since, as is known, the actual anatomical changes are not localized in the pylorus itself but in the distal part of the canalis egestorius section of the stomach. The name »pyloric stenosis» is so widely used and familiar, however, that we may scarcely anticipate any alteration in this particular phrase.

Since the publications of a number of observations, but especially since Wallgren's extensive investigation of one thousand newborn boys all of whom showed normal conditions in the canalis egestorius, we have presumably good reason to question the correctness of the term »*congenital* pyloric stenosis». There may possibly be a congenitally-conditioned predisposition to the muscular hypertrophy which apparently develops rapidly, in certain cases very rapidly, during the first weeks of life and gives rise to the typical clinical picture. Undoubtedly the condition and innervation of the mucous membrane in the canalis play a dominating part in the manifestation of this picture, as is

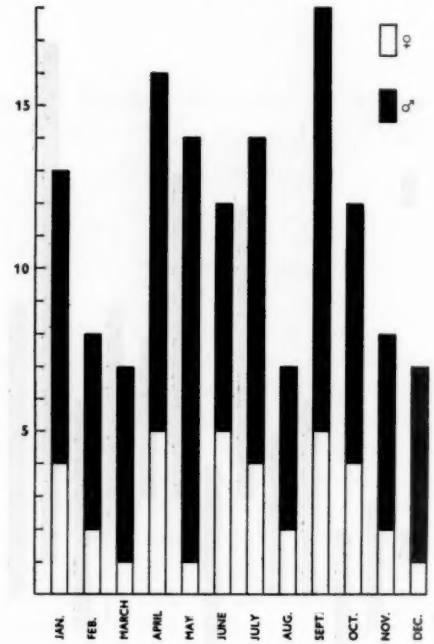
Table 1



clearly indicated by the fact that the hypertrophic, rigid, peristalsis-free part of the canalis remains for a long time, even years, after manifest symptoms of the disease have ceased and regardless of whether or not their disappearance has been conditioned by medical or surgical treatment. I should also like to stress the fact that one occasionally encounters so-called latent cases. In this material there are two such cases, one of which was described by the author in 1939.

A study of the etiology and pathogenesis of this disease seems to reveal two features which deserve more attention than others: first that it is far more common in boys (c. 80 %) and secondly that the period during which the disease is manifest is so sharply

Table 2



limited (the weeks soon after birth). Another special characteristic which appears very distinctly in this series of cases is the frequency of an acute onset, without preceding slight or gradually-developing symptoms of the disease.

From the Scandinavian countries, there are rather large series of cases of pyloric stenosis from Denmark by Monrad, from Finland by Salmi, from Norway by Rinvik, and from Sweden by Faxén.

Table 1 shows the annual distribution in this series from the years 1934—1948. The relatively small figures for the first years are due to the fact that until 1934 almost no infants were treated at the hospital. The table also shows the sex distribution. 73.5 % of the total number of cases were boys and 26.5 % girls,

a proportion which is in good agreement with the c. 80 % boys and 20 % girls which has been found in other countries and at other periods to be relatively constant.

Table 2 shows the distribution among the different months of the year of the times at which the symptoms first appeared. If one may draw conclusions from so limited a series as this, there seems to be a certain accumulation of cases between April and July and possibly during September and October. A similar tendency during the spring months could not be found in a survey of Stockholm cases made earlier by Faxén, but it has been demonstrated in other series, for example Rinvik's series from Norway.

Even if allowance is made for the fact that the number of first-born children is greater than the number born second, third, or later, Table 3 shows that the disease occurs predominantly among first children, particularly as regards girls.

Table 3

Order Among Siblings	♀	♂	Number
I	26 (72 %)	57 (57 %)	83 (64 %)
II	6	31	37
III	2	7	9
IV	2	3	5
V	—	2	2
Total	36	100	136

Table 4 shows that in this series also, the disease was more common among children who at birth were relatively large. This applies especially to girls, not less than 60 % of whom had a birth weight of over 3 500 g (average weight for Swedish girls according to von Sydow 3 361 g). —

The report that pyloric stenosis is particularly common among breast-fed children is undoubtedly related primarily to the appearance of the disease at an age when most children are still at the breast.

Table 4

Weight at Birth	♀	♂	Number
1 501—2 000	—	2	2
2 001—2 500	1	4	5
2 501—3 000	5	8	13
3 001—3 500	9	39	48
3 501—4 000	20	38	58
4 001—4 500	1	7	8
4 501—5 000	—	2	2
Total	36	100	136

60 % ♀ > 3 500 g.
47 % ♂ > 3 500 g.

Table 5

First Symptoms	♀	♂	Number
In First Week..	5 (0)	11 (0)	16 (0)
» Second » ..	5 (2)	16 (4)	21 (6)
» Third » ..	9 (5)	21 (9)	30 (14)
» Fourth » ..	5 (4)	24 (10)	29 (14)
» Fifth » ..	9 (5)	14 (7)	23 (12)
» Sixth » ..	2 (2)	8 (3)	10 (5)
» Seventh » ..	—	2 (0)	2 (0)
» Eighth » ..	1 (0)	3 (0)	4 (0)
> » » ..	—	1 (0)	1 (0)
Total	36 (18)	100 (33)	136 (51)

The figures in parentheses indicate the number of cases in which onset was acute.

Acute onset in c. 12 % in the first week.
» » » » 70 % » » » month.

Table 5 shows the time of onset of the disease, confirming the unanimous reports of others that it usually occurs in the third and fourth weeks and only rarely later than the sixth week. In not less than 12 % of the cases in this series the first symptoms appeared as early as in the first week of life, and in a good 15 % during the second week. The earliest roentgenologically verified

case was that of a thirteen day old girl. Typical roentgen findings were encountered in four other cases as early as the eighteenth, twentieth, and twenty first days of life, respectively. It should be interpolated here that diagnosis or differential diagnosis is based primarily on x-ray examination lege artis of the condition of the canalis egestorius (according to MEUWISSEN and SLOOFF, RUNSTRÖM, particularly the latter), an examination which rapidly and conveniently for both patient and physician gives 100 % certainty as to the presence or absence of pyloric stenosis. It is the author's conviction that examination for palpable or non-palpable pyloric tumour is completely unnecessary, unreliable, time-consuming for the physician, and unpleasant for the patient, whereas an x-ray examination gives the desired information rapidly, indisputably, and conveniently.

What this series shows very plainly is how strikingly often the onset of clinical symptoms is acute. In fifty one cases (38 %), of which eighteen were girls and thirty three boys, it was alleged that vomiting began quite suddenly, and in forty two cases (31 %), twelve of which were girls and thirty boys, the onset could be assigned to a definite day. In six cases it was even possible to give the time of day at which the first violent attack occurred. This sudden and acute onset of the symptoms of the disease in many cases seems to me to suggest that the muscular hypertrophy in the canalis section is not in itself the cause of the appearance of the clinical picture, since it naturally requires some time to develop, even if in some cases only a few days. In several cases with acute onset in my series, I was able to carry out x-ray examinations from a few days up to a week after the appearance of the first symptoms. In one case a 2 cm long typical canal stenosis was established within three days' time; in two cases, 2—3 cm long stenosis within four days' time; in six cases, 3 cm long stenosis within five days' time; and in thirteen cases, 3 cm long stenosis within seven days' time. It seems hardly likely, especially in the cases established within three—five days, that the muscular hypertrophy which is demonstrated in x-ray examination by the appearance of this rigid, peristalsis-free, contracted canalis section could arise in so short a time secondarily to a spasm

induced by mucous membrane changes. On the contrary, these observations seem to me to lend support to the theory that it is the muscular hypertrophy which is primary; further that the disease passes through three phases: a first one in which it is clinically latent, with the primary muscular hypertrophy usually developing rapidly; a second manifest phase brought on by secondary changes in the mucous membrane; and finally a third, again latent, phase with continued muscular hypertrophy of longer or shorter duration (occasionally lasting for many years). If then the muscular hypertrophy is primary, as suggested here, the condition of the mucous membrane and innervation disorders in the canalis undoubtedly play a leading part in the manifestation of the actual vomiting stage. As is known, the point of view most generally accepted hitherto has been that a spasm was the primary factor and the muscular hypertrophy secondary to it. This spasm could be brought on by small lesions or rhagades in the mucous membrane. The fact that even at an early stage in the disease blood has been described as present in the vomit has been regarded as lending support to this theory (ERNBERG, among others). In this material blood was observed mixed with the vomit on one or more occasions in only eleven cases (five girls and six boys). There was blood in the very first vomiting in only two cases. It is very difficult to explain why mucous membrane disorders of the aforementioned type should affect boys so much more than girls.

When the primary muscular hypertrophy, according to the author's view, reaches a certain point, disorders of mechanical or neurogenous type (possibly a combination of the two) arise in the functioning of the mucous membrane. Suddenly or more gradually, these lead the disease over into the manifest stage. As for the pathogenesis of the (according to this process of reasoning) primary muscular hypertrophy, it seems as though it were to be sought in the first place in some maternally conditioned hormonal influence on the child, pre- or postnatal. I believe that Stolte's well-known theory was on the right track, even if his explanation cannot be correct. —

Table 6 shows treatment and treatment results. One hundred and fourteen cases were treated medically; twenty two (16 %),

Table 6

$^{1}/_{1}$ 1934—$^{30}/_{6}$ 1944	Medical Treatment	59	♀ 18, ♂ 41, 1 †[1]
	Surgical »	18 (23 %)	♀ 6, ♂ 12
$^{1}/_{7}$ 1944—$^{31}/_{12}$ 1948	Medical Treatment	55	♀ 10, ♂ 45, 1 †[2]
	Surgical »	4 (5 %)	♀ 2[3], ♂ 2[3]

[1] Nosocomial infection of septic type in the convalescent stage.
[2] Nosocomial infection of cholera infantum type.
[3] All operated on before March 1, 1945.

surgically (operation according to Fredet—Rammstedt). Of the one hundred and thirty six cases, two died (mortality 1.5 %); both were treated medically and died in the convalescent stage of a complicating nosocomial infection. The mortality following surgical treatment was 0.

During the period 1934—June 30, 1944, all the children were first treated medically according to the accepted regimen and with atropine. Those cases which were not noticeably improved within five—six days after this treatment was initiated underwent operation (23 %).

During the remaining period up to and including 1948, all the children were initially treated with scopyl (methylscopolamine nitrate). In 1945 Elgenmark made a preliminary report on this treatment based on some of the cases in this series. Particularly since it has become possible to give this preparation to the children in drop form for perlingual resorption instead of in tablet form for resorption through the mucous membrane of the stomach, the results of this medical treatment have become so good that since March 1, 1945, it has not been necessary to operate on a single case. The scopyl dosage has been one—three drops six times per day twenty—thirty minutes before meals. Subcutaneous injection of the substance has proved necessary in only a few cases. Mild symptoms of intoxication in the form of rapidly transient erythema have appeared in a case or two.

Table 7

Cessation of vomiting upon treatment with 1—3 drops scopyl × 6.

	♀	♂	Total	
After 1 Day	2	1	3	
» 2 Days	—	2	2	
» 3 »	1	6	7	Within 3 Days 12 cases
» 4 »	—	—	—	
» 5 »	1	2	3	
» 6 »	1	2	3	
» 7 »	—	2	2	Within 1 Week 20 cases = 54 %
» 8 »	—	3	3	
» 9 »	—	2	2	
» 10 »	—	—	—	
» 11 »	—	1	1	
» 12 »	1	3	4	
» 13 »	—	1	1	
» 14 »	—	—	—	Within 2 Weeks 31 cases = 84 %
» 15—28 »	2[1]	4	6	
Total	8	29	37	

[1] One patient also had cholera infantum upon admission to the hospital.

Table 7 shows the results of the treatment. In twelve cases the symptoms disappeared very rapidly within three days and in more than half of the cases within one week.

In the majority of cases scopyl treatment (Sol. Skopyl. Pharmacia) seems to me to have a good, powerful effect; it is more efficient, quicker, and less dangerous than treatment with atropine and eumydrine. When one has access to both paediatric and child-surgical experts, operation usually gives results more rapidly and with little or no operation mortality (Donovan, Jacoby, Schaefer and Erbes, among others), but since in many cases medical treatment gives results almost equally rapidly (often within three days), it should always be tried first. In places where there are no such paediatric and child-surgical resources, one may in almost any case gain control over the disease

with internal treatment including scopyl, even if a somewhat longer period of treatment combined with careful isolation is required. In the most severe cases the fluid and protein balance must of course be checked.

Thus in the author's opinion a case of pyloric stenosis should always first be subjected to some days of internal treatment with scopyl. If a rapid improvement fails to take place, whether or not operation should be attempted in the individual case depends on the resources of the place in question for children's surgery.

Summary

1. Survey of one hundred and thirty six cases of pyloric stenosis observed in the years 1934—1948. In twenty two cases (16 %) surgical treatment was undertaken, with no deaths. Mortality for entire series: two cases (1.5 %).

2. With regard to the pathogenesis of the disease, the author suggests that it is to be sought in some perinatal maternal influence on the child (hormonal?) which leads to the rapid postnatal development of muscular hypertrophy in the distal section of the canalis region of the stomach. This hypertrophy leads in its turn to secondary mucous membrane changes which bring about the transition of the disease from the latent to the manifest stage.

3. The author reports on the results of conservative therapy with scopyl solution (methylscopolamine nitrate). This treatment has greatly reduced the need for surgical intervention in this disease.

Résumé

1. Examen de 136 cas de sténose du pylore observés pendant les années 1934—1948. Dans 22 cas (16 %), un traitement chirurgical a été entrepris sans aucune mortalité. Pour la série entière la mortalité est 2 cas (1.5 %).

2. Quant à la pathogénie de la maladie, l'auteur considère qu'il faut la chercher dans une influence périnatale maternelle (d'origine hormonale?) sur l'enfant conduisant au rapide dé-

veloppement postnatal de l'hypertrophie musculaire de la partie distale du canal pylorique. Cette hypertrophie amène à son tour des altérations secondaires de la muqueuse qui provoquent la transition de la maladie du stade latent au stade manifeste.

3. L'auteur rapporte le résultat du traitement conservatif au moyen d'une solution de scopyle (nitrate methylscopolamine). Ce traitement a considérablement réduit la nécessité d'une intervention chirurgicale dans cette maladie.

Zusammenfassung

1. Übersicht über 136 Fälle von Pylorus-Stenose, die in den Jahren 1934—1948 beobachtet wurden. In 22 Fällen (16 %) fand chirurgische Behandlung statt ohne Todesfälle. Gesamtsterblichkeit 2 Fälle (1.5 %).

2. Im Hinblick auf die Pathogenese der Krankheit äussert der Autor den Gedanken an irgend einen perinatalen mütterlichen Einfluss (hormonal?) auf das Kind, der nach der Geburt zu einer überschnellen Entwicklung einer muskulären Hypertrophie im distalen Abschnitt des Pylorus kanales (Canalis egestorius) führen dürfte. Diese Hypertrophie führt wiederum zu sekundären Veränderungen der Schleimhaut, die den Übergang vom latenten Stadium des Leidens zum manifesten Stadium bewirken.

3. Der Autor berichtet über die Ergebnisse bei konservativer Therapie mit Scopyl-Lösung (Methylscopolamin-Nitrat). Diese Behandlung hat die Indikationen eines chirurgischen Eingriffes bedeutend vermindert.

Sumario

1. Se estudian 136 casos de estenosis pilórica observados durante 1934—1948. En 22 (16 %) casos se emprendió tratamiento quirúrgico y no hubo fallecimientos. Mortalidad para series completas: 2 casos (1.5 %).

2. Por lo que se refiere a la patogénesis de la enfermedad, el autor sugiere que se debe buscar en alguna influencia materna perinatal sobre el niño (hormonal?), la cual ocasiona el rápido

desarrollo postnatal de la hipertrofía muscular en la sección distal de la región »canalis» del estómago. Esta hipertrofía ocasiona a su vez alteraciones secundarias de la membrana mucosa, lo que da origen a la transición de la enfermedad del estadio latente al estadio manifiesto.

3. El autor informa sobre los resultados de la terapia conservadora con una solución escopila (nitrato metilescopolamina). Este tratamiento ha reducido considerablemente le necesidad de intervención quirúrgica en esta enfermedad.

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FROM THE PAEDIATRIC CLINIC OF KRONPRINSESSAN LOVISA'S CHILDREN'S HOSPITAL, STOCKHOLM (CHIEF: PROF. A. LICHTENSTEIN) AND THE FOURTH MEDICAL SERVICE OF ST. ERIK'S HOSPITAL, STOCKHOLM (CHIEF: PROF. H. BERGLUND).

Congenital Isolated Pulmonary Stenosis

A Clinical Study of Seven Cases Diagnosed by Heart Catheterization

by

E. MANNHEIMER, Y. LARSSON, T. MÖLLER, H. LAGERLÖF, and L. WERKÖ

As a component in the tetralogy of Fallot, congenital pulmonary stenosis constitutes one of the commonest forms of congenital cardiac malformation. Isolated pulmonary stenosis has, on the other hand, been regarded as relatively rare. Thus out of one thousand cases of congenital cardiac malformation subjected to autopsy, ABBOTT found only nine cases of pure pulmonary stenosis without other cardiac malformations, and TAUSSIG states that she never observed a single one. The majority of authors (ABBOTT; ROSSMAN; CURRENS, KINNEY, and WHITE; AUERBACH and HARPER; GUINSBOURG; KEITH; MANNHEIMER) consider isolated pulmonary stenosis a severe type of congenital cardiac malformation which may be caused by foetal endocarditis. Unlike the tetralogy of Fallot, in which the stenosis is infundibular, this type may be the result of an inflammatory process with secondary fusion of the pulmonary cusps themselves. Among the eleven cases published by CURRENS, KINNEY, and WHITE in 1945, all of which underwent autopsy, there were some less severe cases which were free of symptoms and did not die as a result of their congenital cardiac malformation. POLLACK, TAYLOR, ODEL, and BURCHELL (1948) have been the first to publish the results of heart catheterization in cases of isolated pulmonary stenosis, and in one of the three cases they describe there were no subjective

symptoms. Of the two others, one showed signs of subacute septic endocarditis and the other symptoms of active rheumatic carditis.

Simultaneously with the preparation of this article, GREENE AND ASSOCIATES of the Bellevue and Presbyterian Hospitals in New York published four cases of pure pulmonary stenosis and four of idiopathic pulmonary dilatation studied by means of heart catheterization. All were cases of children or young persons without subjective symptoms. In the cases of pulmonary stenosis the blood pressure in the pulmonary artery was normal but considerably elevated in the right ventricle, while in the cases of idiopathic pulmonary dilatation the pressure in the right ventricle was normal or only slightly elevated, with the pulmonary pressure somewhat lower. The corresponding clinical features were a weak or inaudible second pulmonary sound in the stenosis and a strongly accentuated second pulmonary sound in idiopathic pulmonary dilatation.

Upon visualization of pulmonary stenosis by means of angiocardiography, SUSSMAN, GRISHMAN, and STEINBERG found poststenotic dilatation of the pulmonary artery in certain cases.

Virtually all authors point out that in these cases the electrocardiogram shows right axis deviation. It is also alleged that a prolonged systolic murmur over the pulmonary orifice and late cyanosis are typical clinical signs.

Thus isolated pulmonary stenosis has with occasional exceptions been regarded as a rare and very severe form of congenital cardiac defect with so few differentiating symptoms that it has usually not been possible to diagnose it during the patient's lifetime. In the course of systematic studies of one hundred congenital cardiac malformations by means of heart catheterization we have found seven cases of isolated pulmonary stenosis in a short time, however. Simultaneously TYBJERG-HANSEN AND ASSOCIATES in Copenhagen, using the same methods, have also observed seven similar cases.

As the clinical picture in these cases has deviated from the earlier conception of isolated pulmonary stenosis we thought these seven cases worth recording. Their chief characteristics have been the absence of cyanosis and of limitation of activity. Further-

more, these cases have a loud systolic murmur of maximal intensity over the pulmonary orifice, a typical x-ray picture with bulging pulmonary arc, pathological electrocardiographic findings with a right axis deviation, and normal arterial oxygen saturation. Upon heart catheterization low or normal blood pressure has been found in the pulmonary artery, hypertension in the right ventricle, and no signs of intracardiac shunts.

Methods

For the *recording* of electrocardiograms, phonocardiograms, and intracardiac pressure curves an ELMQVIST system, Triplex-type electrocardiograph has been used. This instrument makes possible simultaneous recording of five tracings. *Heart catheterization* was carried out according to COURNAND and the intravascular pressure measured with TYBJERG-HANSEN's and WARBURG's apparatus. *Calibrated phonocardiography* according to MANNHEIMER and STORDAL has been used to record the sound phenomena of the heart. *Angiocardiography* has been performed under narcotal anesthesia with 70 % diodrast according to SUSSMAN AND ASSOCIATES, with a cassette changer designed by ULF-SPARRE. The heart volume was determined according to JONSELL. The *standard exercise test* was carried out according to COURNAND and RICHARDS as used by BING. *Hypoxia tolerance test* 9 % oxygen for 10 minutes was performed according to MANNHEIMER.

Results

Table I includes six females and one male aged six—twenty five years. These seven persons all appeared at first to be completely well. None of them was cyanosed and their subjective symptoms consisted only of slight dyspnoea and palpitations after exertion in three cases. Except in Case 5, who was obese, height and weight were within normal limits. One woman (Case 7) was in the third month of pregnancy. In all seven cases the diagnosis of a cardiac defect was established in the routine medical examination, in two cases in the neonatal period.

Physical examination of the heart showed no enlargement. In all seven cases a very marked systolic murmur was heard over the whole heart. In every case but one (Case 2) this sound was of maximal intensity over the pulmonary orifice. *Fig. 1* shows the electrocardiogram and calibrated phonocardiogram from Case 3.

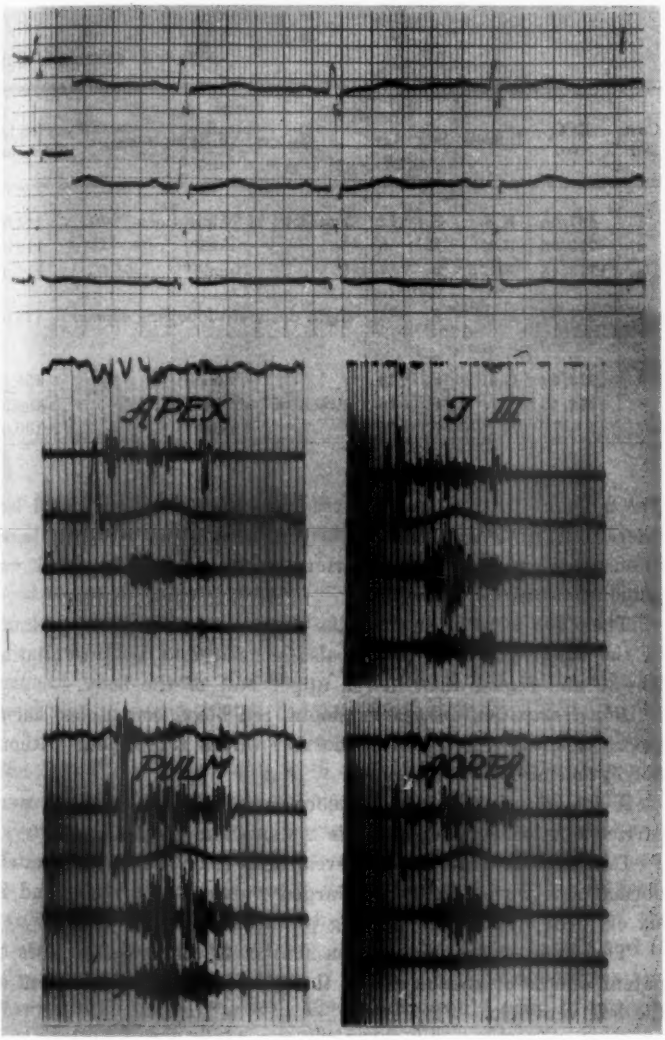

Fig. 1. The electrocardiogram and phonocardiogram in Case 3.

Table 1

7 cases of congenital isol

Case No.	ECG No.	Initials	Sex	Age	Subjective Symptoms	Height in cm	Wt. in kg
1	667/48	K.S.	F.	12	3 attacks of palpitations	144.0	39.5
2	775/48	B.M.	M.	6	none	118.5	21.7
3	1112/48	A.L.F.	F.	7	none	114.0	19.5
4	971/47	E.B.	F.	25	slight dyspnoea following exertion	178.0	60.1
5	329/40	G.J.	F.	23	none	156.5	62.9
6	272/48	S.J.	F.	16	attack of palpitations	160.0	52.3
7	—	M.P.	F.	24	none	160.0	55.2

The murmur in this case was recorded over the apex, third left intercostal space, pulmonary artery, and aorta. It was most intense over the pulmonary artery, where a systolic thrill was palpated.

The *blood pressure* in the arms was normal. The blood pressure in the lower extremities was also normal and by auscultation 20—30 mm higher than in the upper half of the body.

Blood examination (haemoglobin, red blood corpuscles, haematocrit reading, etc.) showed normal values throughout without polycythaemia.

X-ray examinations, both fluoroscopic and radiographic, were carried out in every case. *Table 2* shows the results.

In all cases fluoroscopy revealed a heart of approximately normal size with distinctly enlarged pulmonary arteries and in six of them a markedly bulging pulmonary arc.

The fluoroscopic picture was similar to that seen in cases of patent ductus arteriosus except that there was no enlargement of the left ventricle.

Radiography complemented fluoroscopy and in addition made possible determination of the heart volume. This lay within nor-

1

isolated pulmonary stenosis.

Murmur	Maximal Point	Blood Pressure		Blood		Remarks
		Arm	Leg	Hgb.	RBC	
loud systolic	pulm.	135/80	165/90	96	4.82	
»	I III sin.	95/65	110/75	84	4.21	
»	pulm.	125/75	165/70	80	4.17	frequently recurring respiratory tract infections
»	»	125/85	—	80	3.9	exploratory thoracotomy at age of 19 for suspected patent ductus arteriosus
»	»	125/85	—	94	4.8	obesity
»	»	125/90	—	86	4.6	
»	»	135/75	—	84	4.2	pregnancy, 3rd month

mal limits in all cases except for Case 2 in which we found it to be somewhat increased (410 cc/m^2 body surface). *Fig. 2* shows the x-ray picture in Case 4.

Angiocardiography was performed in three cases. *Fig. 3* shows two pictures from Case 1 taken two and seven seconds after the injection. They show a distinct infundibular stenosis and pronounced poststenotic dilatation. In Cases 2 and 3 the stenosis could not be demonstrated by angiocardiography.

In all cases the electrocardiogram showed a right axis deviation (see *Fig. 1*). In Cases 1—5 and 7 this was moderately pronounced, with the angle of the electric axis between 90° and 115° (average 103°). In Case 6 the right deviation of the electric axis increased from 115°—135° between the ages of eight and thirteen. For purposes of comparison, it may be pointed out that in forty two children aged thirteen with normal hearts the angle of the electric axis was on the average 58° ± 3.0° (MANNHEIMER) and in fifty cases with the tetralogy of Fallot 122° (HERDENSTAM and MANNHEIMER — see *Fig. 4*). The results would seem to indicate that in these cases right axis deviation is considerably less pronounced than in the tetralogy of Fallot.

Table 2

X-ray and electrocardiography.

Case No.	Size of Heart	Cardiothoracic Index	Heart Volume cc/m² Body Surface	Pulm. Arc	Angle of Axis on ECG
1	normal	0.51	300	bulging	110°
2	enlarged	0.59	410	»	100°
3	normal	0.52	290	»	90°
4	»	0.41	320	»	100°
5	»	0.44	345	normal	115°
6	»	—	340	bulging	115°—135°
7	»	—	—	»	90°

Except for the right axis deviation, the electrocardiogram showed no pathological features.

In Cases 1 and 3 the hypoxia test was positive, with slightly lowered S—T intervals during the test. In Case 2 the hypoxia test was normal. In the four others it was not made.

Heart Catheterization. Cases 1, 2, and 3 were catheterized at Kronprinsessan Lovisa's Children's Hospital; Cases 4, 5, and 7 at St. Erik's Hospital; and Case 6 at Sabbatsberg Hospital.[1]

In six of the cases intracardiac pressure curves were recorded, while in Case 6 only the mean pressure was measured with a water manometer.

The results of the intracardiac pressure measurements and blood gas analyses are given in *Tables 3* and *4*.

Table 3 shows that in all cases the blood pressure was considerably lower in the pulmonary artery than it was in the right ventricle. The pressure in the pulmonary artery varied from 15/0 to 30/14 mm Hg and thus remained within the normal range of variation, while the pressure in the right ventricle showed a definite increase in all cases, varying between 170/0 and 58/9 mm Hg. It is this difference in pressure between the right ventricle and pulmonary artery which justifies the diagnosis of pul-

[1] The authors wish to thank Dr. Å. Frisk and Dr. Th. Wiklund for permitting them to use the results of their examinations in Case 6.

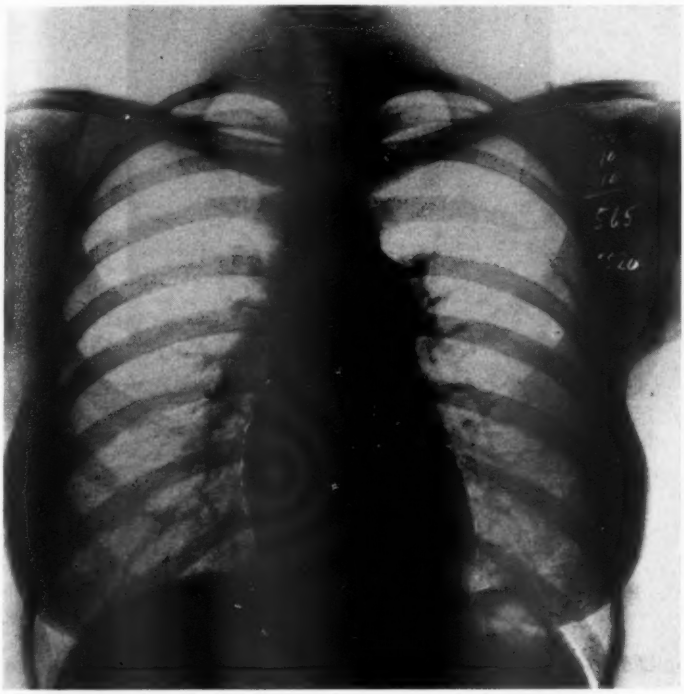

Fig. 2. X-ray picture of the heart, A—P view. 25 year old woman.

monary stenosis. *Figs. 5* and *6* provide examples of intracardial pressure curves in Cases 2 and 4. They bear a noticeable resemblance to those found in cases of the tetralogy of Fallot. The slight difference which exists lies in the fact that the pressure in the pulmonary artery in cases of the tetralogy of Fallot is usually lower than in these cases of isolated pulmonary stenosis. The pressure in the right ventricle, on the other hand, is usually the same or higher in isolated pulmonary stenosis than in the tetralogy of Fallot and in the former condition bears no relationship to the pressure in the aorta as it may do in cases where there is an overriding aorta.

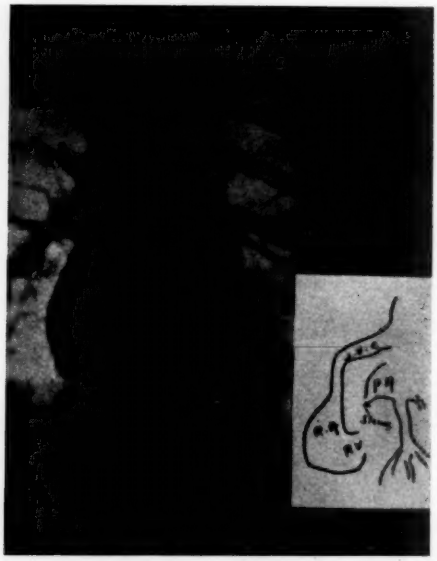

Fig. 3 A. Angiocardiography in Case 1, 2 seconds after injection.

Table 4 gives the results of the blood gas analyses. There was no regularly recurrent difference in oxygen content between the superior vena cava and the right auricle or between the right auricle and ventricle, a circumstance which eliminates the diagnosis of auricular or ventricular septal defects. In all cases, on the other hand, there was a slight but regular difference in oxygen content between the right ventricle and the pulmonary artery; the blood in the latter was richer in oxygen. The difference amounted to at most 1.5 vol.% (Case 5) and at least 0.2 vol.% (Case 4). Only in Case 5 was the difference so great that it exceeded the limit for normal variation (1.2 vol.% according to LAGERLÖF, MANNHEIMER, and WERKÖ).

In patent ductus arteriosus there is a higher oxygen content in the pulmonary artery. This malformation may nevertheless be excluded in these cases on the following grounds. As yet lower

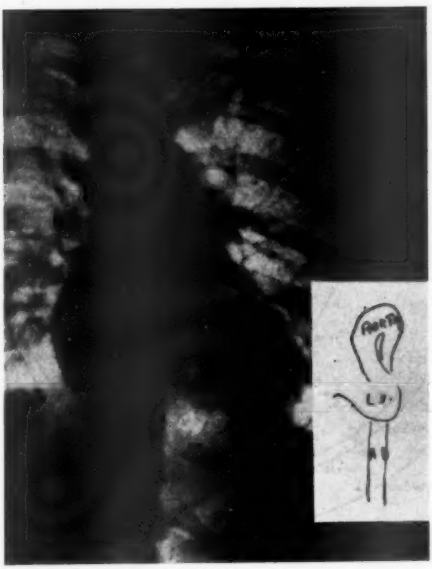

Fig. 3 B. Angiocardiography in Case 1, 7 seconds after injection.

pressure in the pulmonary artery than in the right ventricle has not been observed in a single catheterized case of patent ductus arteriosus. There was no continuous murmur in any of our cases. In Case 4 exploratory thoracotomy was performed (CRAFOORD) six years before catheterization upon suspicion of patent ductus arteriosus. The operation revealed only a widened pulmonary artery, however. The presence of a small septal defect at or above an infundibular stenosis cannot be excluded in cases where the oxygen content of the pulmonary artery exceeds that of the right ventricle. Such a small septal defect is, however, of no functional importance. The pulmonary stenosis dominates the picture. The arterial oxygen saturation (see *Table 4*) was normal in Cases 1—5, in which it remained between 93 and 96 %. In Case 6 it was lower (86 %), which is surprising as the patient was wholly acyanotic. Inasmuch as a work test also showed the

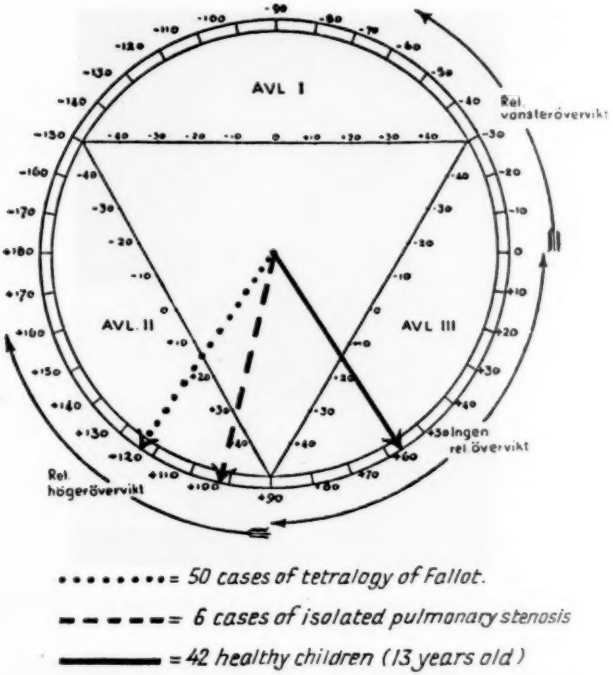

Fig. 4. Angle of electric axis.

same arterial oxygen saturation before as after work, it is improbable that there was any venous-arterial shunt in this case. The lower saturation value may have been due to some technical error.

In Cases 1—4 the »standard exercise test» (COURNAND and RICHARDS, BING) was performed. The results showed normal conditions with an increase in the amount of oxygen consumed per minute and per liter ventilation during work. From this the conclusion may be drawn that in these cases the pulmonary stenosis did not effect the pulmonary circulation in such a way that the gaseous exchange was impaired. In this respect also there is an important difference between this disease and the tetralogy of

Fallot, in which the oxygen values sink in connection with work (BING, GRAF and MANNHEIMER).

Table 3

Heart catheterization. Intracardiac blood pressure in mm Hg.

Case No.	Pulmonary Artery			Rt. Ventricle			Rt. Auricle
	Syst.	Diast.	Mean Press.	Syst.	Diast.	Mean Press.	
1	17	4	—	170	0	49	7
2	15	0	—	72	0	—	6
3	30	14	—	94	6	60	10
4	18	9	12	58	9	18	4
5	21	7	12	116	15	28	4
6	—	—	13	—	—	46	—
7	17	9	12	95	4	36	2

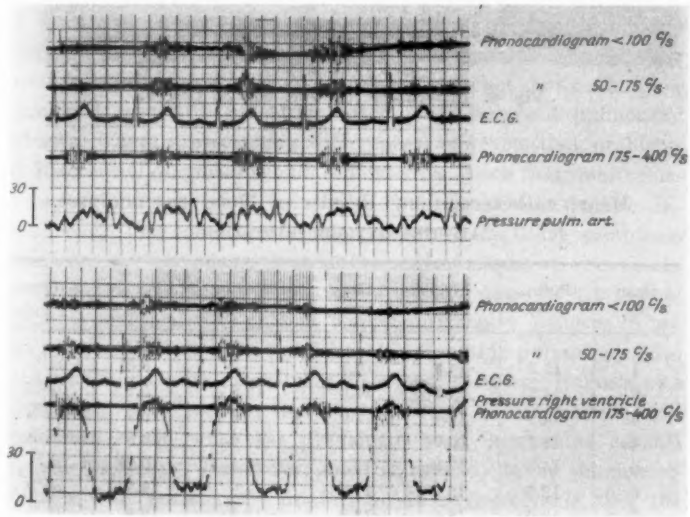

Fig. 5. Intracardiac pressure curves: Case 2.

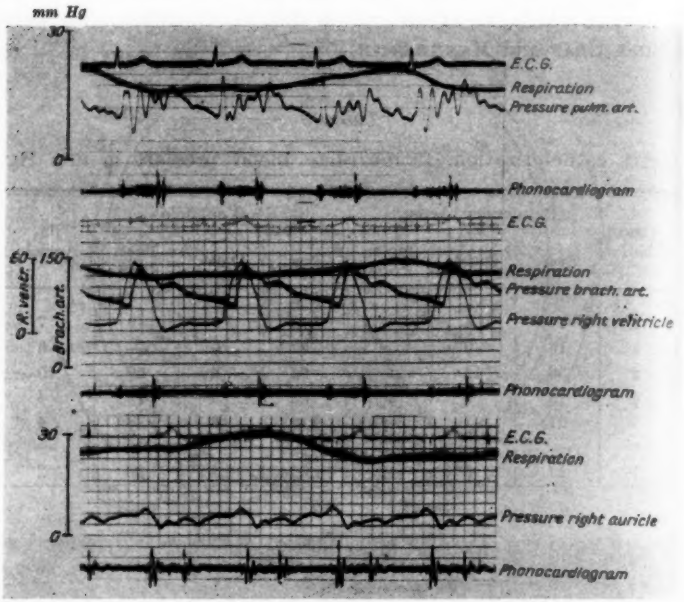

Fig. 6. Intracardiac pressure curves: Case 4.

Table 4

Heart catheterization. Results of blood gas analyses. Arterial oxygen saturation.

Case No.	Pulm. Art.	Rt. Ven.	Rt. Aur.	Superior Vena Cava	Fem. Art.	Arterial O_2 Sat.
1	15.2	14.3	14.1	—	18.6	94 %
2	14.7	13.2	14.0	12.6	15.7	94 %
3	14.8	13.7	12.9	13.6	19.4	96 %
4	13.1	12.9	13.1	12.0	16.8[1]	93 %
5	15.3	13.8	15.1	14.4	19.2[1]	93 %
6	12.5	12.2	12.9	11.9	18.3	86 %
7	13.9	13.0	13.0	13.4	16.6	94 %

[1] brach. art.

Differential Diagnosis

In differential diagnosis the following congenital heart defects must be considered: patent ductus arteriosus; auricular septal defect; Lutembacher's syndrome (congenital mitral stenosis + auricular septal defect); and idiopathic pulmonary dilatation. Finally the isolated malignant pulmonary stenosis as it has hitherto been understood should be differentiated from the benign disease described here. The clinical features of these two forms are quite different, with cyanosis and limitation of activity in the former and absence thereof in the latter, but anatomically the difference is apparently one of degree only. It is possible that the benign form may become malignant.

The form of pulmonary stenosis described here resembles patent ductus arteriosus in the following particulars: absence of cyanosis, capacity for normal activity, and bulging pulmonary arc. The absence of a continuous »machinery» murmur and the results of intracardiac pressure measurements exclude patent ductus.

Auricular septal defects and the Lutembacher syndrome resemble benign pulmonary stenosis in two respects: namely, they occur in acyanotic patients and x-ray examination shows a bulging pulmonary arc with pulsating, often much enlarged pulmonary arteries. There are so many differences, however, that problems of differential diagnosis should seldom arise. Both these malformations are characterized primarily by infantilism, cardiac insufficiency, and considerable enlargement of the heart, symptoms which are not attendant upon pulmonary stenosis.

As far as idiopathic pulmonary dilatation goes, its symptomatology is identical with that of benign pulmonary stenosis. Since the intracardiac pressure conditions in idiopathic pulmonary dilatation have not been extensively described except by GREENE AND ASSOCIATES, it is possible that further heart catheterization will sometimes reveal what has previously been interpreted as this disease (SUSSMAN, GRISHMAN, and STEINBERG) to be pulmonary stenosis with poststenotic dilatation. It is conceivable that the stenosis is primary and the poststenotic dilatation secondary. Similar conditions are encountered in other malformations within

the vascular system, as for example in the tetralogy of Fallot and certain cases of coarctation of the aorta.

Summary

Seven cases of congenital benign isolated pulmonary stenosis are described. They have displayed a uniform clinical picture with the following principal features.

1. Normal physical development without signs of cyanosis or cardiac decompensation.

2. A prolonged, very loud systolic murmur over the pulmonary orifice.

3. Stenosis of the infundibular part of the pulmonary artery. This may be established by heart catheterization and in some cases by angiocardiographic visualization.

4. X-ray findings: a bulging pulmonary arc and enlarged pulmonary arteries.

5. A moderate right axis deviation on the electrocardiogram.

The haemodynamics and differential diagnosis in these cases have been discussed.

Résumé

Sept cas de sténose isolée de l'artère pulmonaire sont décrits. Nos cas ont montré les symptomes suivantes:

1. Developpement physique normal, sans signes de cyanose ou de décompensation cardiaque.

2. Murmure systolique très bruyant et prolongé au niveau de l'orifice de l'artère pulmonaire.

3. Sténose de la partie infundibulaire de l'artère pulmonaire. Ceci peut se prouver par la cathétérisation du cœur et dans quelques cas par l'angiocardiographie.

4. Radiographie: un conus de l'artère pulmonaire bombé et des artères pulmonaires dilatées.

5. Une petite déviation vers la droite de l'axe de l'électrocardiogramme.

Zusammenfassung

Sieben Fälle angeborener gutartiger isolierter Pulmonal-Stenose sind beschrieben. Sie zeigen folgende Merkmale:

1. Normale physische Entwicklung ohne Zeichen von Cyanose oder Herzdekompensation.

2. Ein verlängertes, sehr lautes systolisches Geräusch über der Pulmonalis.

3. Stenose des infundibularen Teils der Arteria Pulmonalis. Das kann durch Katheterisierung des Herzens und in manchen Fällen durch Angiocardiographie festgestellt werden.

4. Röntgenbefund: Ausbuchtung und Vorwölbung des Conus Pulmonalis und Verbreiterung der Pulmonalarterie.

5. Das Elektrokardiogram zeigt eine mässige Deviation nach rechts.

Die Differentialdiagnose in diesen Fällen wird diskutiert.

Sumario

Se describen 7 casos de Estenosis Pulmonar congenita aislada. Nuestros casos presentaron un cuadro bastante uniforme de la enfermedad, con los siguientes razgos fundamentales.

1) Desarrollo fisico normal sin sintomas de cianosis o descompensación cardiaca.

2) Un soplo sistolico muy fuerte y prolongado a nivel del orificio de la arteria pulmonar.

3) Estenosis de la parte infundibular de la arteria pulmonar. Esto puede establecerse por cateterización del corazon y en algunos casos por visualización cardiografica.

4) A los rayos X se encuentra un cono pulmonar saliente y ensanchado. En este respecto difieren estos casos considerablemente de la estenosis pulmonar de la tetralogia de Fallot, en la cual el contorno del cono pulmonar es concavo y no se constatan pulsaciones.

5) Desviación moderada hacia la derecha del electrocardiograma.

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FROM THE STATE BACTERIOLOGIC LABORATORY AND THE PAEDIATRIC CLINIC OF KAROLINSKA INSTITUTET AT KRONPRINSESSAN LOVISA'S CHILDREN'S HOSPITAL, STOCKHOLM

An Attempt to Immunize Small Children with Pneumococci

by

GUNNEL MELIN

During the past fifteen—twenty years attempts to immunize against pneumococcic infections, especially pneumococcic pneumonia, have been made on a relatively large scale, particularly in the United States. A number of research workers, for example LISTER and ORDMAN (1) and CECIL and AUSTIN (2), have used killed bacteria as antigenic agents, while others, such as FELTON (3) and MAC LEOD, HEIDELBERGER, and co-workers (4—6) have used specific capsular polysacharides.

These attempts at immunization, which have all been made on adults, appear on the whole to have given favourable results as to both the serologic antibody response and the clinical effect.

Similar investigations, made on children with a vaccine, consisting of heat-killed pneumococci by HODES, ZIEGLER, and ZEPP (7) have shown that children under two years of age react with little or no antibody formation, while in older children it is possible to obtain a fairly good antibody response.

In clinical and bacteriological studies of acute upper respiratory tract infections in pre-school children attending day-nurseries during the years 1946—1948 MELIN (8) showed that such children aged one—three have a marked tendency to contract protracted and repeated upper respiratory tract infections which are apparently caused by pneumococci. In this series of cases 70 per cent of the pneumococci found belonged to one of types 6, 11, 19, 23, and 17 and a further 14 per cent one of types 14, 15, and 7 (see Fig. 1).

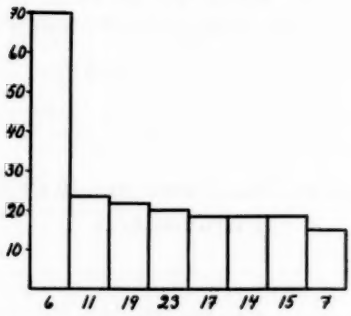

Fig. 1. Types of pneumococci among day nursery children.

Inasmuch as the infections seemed notably contagious and in addition lasted so long that they caused considerable inconvenience both to the children and to their working mothers, it seemed worthwhile to attempt by inoculation to stimulate the organisms capacity for forming antibodies to combat the bacteria in question. Simultaneously a study of the children's humoral antibody response to the inoculation was carried out.

Case Material

In October—November 1948 a total of ninety-three children and ten adults were inoculated. The children had attended the HSB Day Nurseries in Stockholm and most of them were members of groups of one—three years olds. A small group aged six months—one year and a somewhat larger group consisting of four—six years olds were also inoculated. The ten adults were Nursery Personnel who had requested inoculation. The sizes of the different groups are shown in table I.

Methods

The vaccine used contained pneumococci of types 6, 7, 11, 14, 15, and 23. Types 17 and 19 could not be included for technical reasons. The pneumococci were cultivated for forty-eight hours in broth at 37°, after which the broth was centrifugated and the bacteria suspended in physiologic saline solution to which 0.1 ‰ merthiolate and 2 per cent formalin were added, the latter to kill the bacteria. Equal quantities of each type were used and the volume of the vaccine was so adjusted that 1 ml represented approximately 6 000 million organisms.

0.2, 0.4, and 0.8 ml of the vaccine were given subcutaneously at weekly intervals. In a few cases the same quantity of vaccine was administered in four injections.

Blood was drawn from each child before the first and one week after the last injection.

For estimating the antibody content of the blood the object glass agglutination and capsular swelling method, described by LÖFSTRÖM (9) was used.

Results

Of the one hundred and three inoculated, almost all had light local reactions disappearing in a few days. Seventeen cases exhibited rise in temperature usually up to 38°, but in two cases above 39°. These symptoms set in eight—twelve hours after the third injection and gradually disappeared after a further twelve hours. They were noted for the most part among the older children and adults. In not a single case were there general reactions in children under two years of age and in this group also the local reactions were weakest.

In the blood drawn before inoculation antibodies could be demonstrated in only one case — that of a three year old girl who displayed in her first sample antibodies against type 7 in a serum dilution of $^1/_4$. The presence of these antibodies might possibly have had some connection with an acute pharyngeal infection with fever which she had two weeks before the bleeding was done.

As Table I shows, forty-six of the one hundred and three inoculated had antibodies in serum after inoculation. Of these sixteen were from the group of twenty-two children over three years of age and eight from the ten adults, the remaining twenty-two were from the seventy-one children under three years of age. In other words, 75 per cent of the inoculated belonging to the group »Children Over Three» + »Adults» and 31 per cent of the inoculated belonging to the group »Children Under Three» reacted to the inoculation with antibodies. Fig. 2 shows the percentual number of antibody responses within the different age groups. As may be seen, a diagram was obtained in which the lowest values signify the lower age groups.

Table I

Antibodies in the different age groups

Age	<1	1	2	3	4	5–6	Adults	Total
Children	5	11	25	30	16	6	10	103
Antibodies	1	1	7	13	11	5	8	46
Pn 6	1	1	2	7	1	1	2	15
Pn 7	1	—	—	3	4	—	4	12
Pn 11	—	—	1	4	3	1	2	10
Pn 14	—	—	4	5	7	2	3	21
Pn 15	—	—	—	—	2	—	—	2
Pn 23	—	—	—	—	1	2	—	3

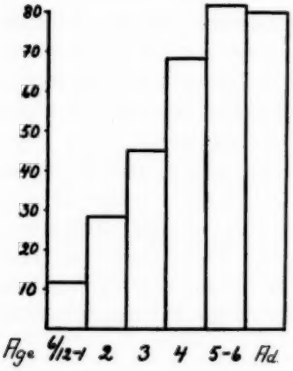

Fig. 2. Percentual number of antibody responses within the different age groups.

Antibodies could be demonstrated in only two cases in a serum dilution higher than $^1/_4$. In both of these cases the dilution was $^1/_8$. One was a case of a three year old girl who had antibodies in serum before inoculation and the other was one of the adults, who responded to pneumococcus type 6 with this relatively high titre.

Table I also shows the number of sera within the different age groups in which antibodies against the different types were found. The majority who reacted with antibody formation showed

these against only one or two types. A few children and one adult reacted against three types, but no one against more. The types which gave the best antibody responses were 6 and 14.

Discussion

The results indicate that the humoral antibody formation against the pneumococcus types used here was considerably poorer in children under three than in older children and adults. In the two latter groups conditions seem on the whole to be similar. The youngest children also showed lesser general and local reactions following inoculation than the older children and the adults.

These results correspond very well with those reported by HODES and co-workers (7) from a similar investigation in Baltimore. Using the mouse protection test, the authors were able to show that the antibody response to inoculation with killed pneumococci of types 1 and 6 was much poorer in children under two than in older children.

It is conceivable that the younger children's poorer capacity for forming humoral antibodies is a factor which contributes to giving their respiratory tract infections the typical clinical picture: long-drawn-out superficial infections of which the organism seems to find it hard to rid itself.

It is also noteworthy that types 6 and 14 in the vaccine gave the best antibody reactions. According to both American investigations reported by HEFFRON (11) and Swedish investigations reported by MELIN (8), it is these two types among those in the vaccine which are most likely to give rise to pneumonia in children. This is in line with LÖFSTRÖM's (9, 10) observation that the pneumococci, which have the strongest antigenic qualities are usually the most likely to give rise to pneumonia.

The results reported here show only the body's humoral antibody response to inoculation. It is known from a large number of investigations that there is a certain parallelism between the humoral antibody titre and the organism's power of resistance, but there are many cases in which immunization attempts have given good clinical results in spite of the fact that humoral anti-

body reactions could not be demonstrated. — With regard to the clinical results of this attempt at immunization one may perhaps expect them to be better for the small children than the antibody responses indicate. Everything indicates, however, that younger children react more poorly than older children and adults to the antigens used here. To draw general conclusions from this concerning the younger organisms antibody-forming capacity would probably be an error however we know that even small children and infants react promptly and adequately with antibodies against, for example, beta streptococci and aureus staphylococci (LAURELL, MELIN 12, 13). It is also known from CARLENS' (14) investigations that small children have more resistance to and form better antibodies against type 3 pneumococci than older children and adults.

The cases reported on here constitute merely the beginning of a planned investigation of immunity against pneumococci of different types in children of different ages. Hence the material is decidedly limited and the method used for determining the antibodies in the blood is a rather rough one. The author has felt it of value, however, to obtain a general conception of conditions before starting to employ on a larger series of cases one of the more complicated methods for more exact antibody determination which is given in the literature.

In a coming paper a report will be presented on the clinical results and the effect of the inoculations on the carrier rate among the children.

Summary

Ninety three children aged six months—six years and ten adults were inoculated with vaccine containing killed pneumococci belonging to types 6, 7, 11, 14, 15 and 23. The humoral antibody titre against these types was studied before and after inoculation by examination of object glass agglutination and capsular swelling according to LÖFSTRÖM.

In children under three years of age humoral antibodies have appeared to a considerably lesser extent following inoculation than in older children and adults. In this respect good agree-

ment has been obtained with the results of similar American investigations.

The connection between the deficient formation of immune bodies in younger children and the frequent occurrence in them of protracted upper respiratory tract infections is discussed.

Résumé

93 enfants d'un âge de 6 mois à 6 ans et 10 adultes, ont été vaccinés par un vaccin contenant des pneumococces des types 6, 7, 11, 14, 15 et 23, qui on été tues. Les dosages des taux d'anticorps spécifiques, contre ces germes, avant et après la vaccination, ont été effectués par les méthodes de Löfström.

Après la vaccination, chez des enfants de moins de 3 ans, on à trouvé les anticorps dans une quantité beaucoup moindre, que chez les enfants plus agés et chez les adultes. A ce sujet il est interessant de signaler que nous avons trouvés des résultats très semblables à ceux des travaux américains.

On discute le rapport entre l'incapacité, chez les petits enfants, de former des anticorps et leurs infections des voies réspiratoires souvent tenaces.

Zusammenfassung

93 Kinder im Alter von einem halben bis sechs Jahren und 10 Erwachsene sind mit einem Vaccin geimpft worden, das abgetötete Pneumokokken enthielt, die den Typen 6, 7, 11, 14, 15 und 23 angehören. Der humorale Antikörpertiter gegen diese Typen ist durch die Untersuchung von Objektglasagglutination resp. Kapselschwellung nach Löfström vor und nach der Impfung studiert worden.

Bei Kindern unter drei Jahren sind nach der Impfung humorale Antikörper in bedeutend geringerem Umfange aufgetreten, als bei älteren Kindern und Erwachsenen. In dieser Beziehung sind gute Übereinstimmungen mit den Ergebnissen von gleichen amerikanischen Untersuchungen erzielt worden.

Der Zusammenhang zwischen der unzureichenden Immun-

körperbildung bei jüngeren Kindern und dem üblichen Befund bei denen mit langwierigen oberen Luftwegsinfektionen wird diskutiert.

Sumario

A 93 niños de una edad comprendida entre seis meses y seis años y a 10 adultos se les ha hecho una inoculación vaceínica de una vacuna que contenía neumococos de los tipos 6, 7, 11, 14, 15 y 23 que han sido distruídos. Las dosis de los tipos de antídotos específicos de estos gérmenes, antes y después de la inoculación han sido efectuadas por los métodos de Löfström.

Después de la inoculación, en el caso de los niños de menos de tres años se han encontrado los antídotos en una cantidad mucho menor que en los casos de los niños de más edad y en los de los adultos. A este respecto es interesante haber encontrado resultados muy parecidos a los de los trabajos americanos.

Se discute el resultado sobre la incapacidad, en el caso de los niños de corta edad, de formar antídotos y sus frecuentemente tenaces infecciones de las vías respiratorias.

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FROM THE PAEDIATRIC CLINIC OF KRONPRINSESSAN LOVISA'S CHILDREN'S HOSPITAL, STOCKHOLM.
CHIEF: PROF. A. LICHTENSTEIN.

The X-Ray Appearance of the Knee Joint in Obese Overgrown Children

by

HANS-OLOF MOSSBERG, M.D.

In the second decade of the twentieth century CZERNY pointed out in his lectures (cf. KELLER 1927) that obesity is only one part of a growth process which goes on both in breadth and length. He called this double process *gigantism*. KELLER (1927, 1929) dealt with this question extensively and came to the same conclusion. ROSENSTERN (1931) also verified the statement of these authors that there is often a large skeleton in obese children. He then compared the wrist measurements of obese children with the mean values of normal children of the same age. OPITZ (1933) emphasized that the bones of the knee joint are unusually large.

In estimating the development of the skeleton none of these authors, however, considered the total bodily development of the obese child, that is the physiological age, nor the fact that the development of obese children must be compared with that of children of normal weight with the same degree of physiological development before it can be called excessive. On this basis chronological age should not be used in the comparison of obese and normal children as it was by these authors.

In order to compare obese and normal children, we require a method by which physiological age may easily be assessed. This has already been worked out, and obese overgrown children have been compared with, among other things, normal children of the same height. For the purposes of this paper the physiological age of a child has been assessed from his height by reading back from tables showing the normal height for age.

During the last ten years it has been shown that in both their bodily and mental development obese children are on the average in advance of normal children of the same age (BRUCH 1939, MOSSBERG 1948, and others).

When height forms the basis for assessment of the number of years by which the obese child is in advance of normal development, it appears that the degree of development of these children is in no way different from that of normal children of the same height. This is valid for the skeletal development. It may be supposed that the bones of the knee joint will not differ in either obese or normal children if the physiological age is taken as a basis for comparison. It was to analyze this question that this investigation was made.

Normal Appearance of the Knee Bones

As measurements of the breadth of the bones of the knee in normal Swedish boys and girls were lacking, normal material was collected.

Material and Methods

From the x-ray departments at Kronprinsessan Lovisa's Children's Hospital, the Serafimer Hospital, and St. Göran's Hospital, all of Stockholm, seven hundred sixteen roentgenograms of cases (three hundred eighty boys, three hundred thirty six girls) aged one to twenty years with suspected or certain bone fractures were collected and statistically analyzed.

The x-ray technique was identical in the three hospitals. The focus-film distance varied between 70 and 85 cm. This, together with the varying thickness of the knee from one case to the next, that is the variation in the bone-film distance, had an influence of about $\pm$ 2 % in the sizes of the bone shadows on the roentgenogram. This is not significant, since the normal limits ($\pm 3\sigma$) were found to be about $\pm$ 20 % of the normal mean value (see Table 1).

The material is divided into two-year age groups. In measuring the bones of the knee in the frontal (antero-posterior) x-ray

Table 1.

Normal values in millimeters for the greatest breadth of the diaphyses and epiphyses of the knee joint on the roentgenogram for boys and girls from 1 to 20 years.

Age Group	Diaphysis of Femur			Epiphysis of Femur			Epiphysis of Tibia			Diaphysis of Tibia		
	n	M	σ	n	M	σ	n	M	σ	n	M	σ
Boys												
1— 2	39	47.9	4.8	39	33.4	6.8	39	26.6	4.0	39	38.3	3.8
3— 4	36	58.0	4.7	36	50.6	7.0	36	38.1	6.4	36	46.6	4.0
5— 6	39	62.5	3.7	39	60.5	4.8	39	47.7	6.2	39	50.6	2.7
7— 8	38	67.5	3.3	38	68.6	3.6	38	58.6	5.6	38	55.9	3.6
9—10	40	73.1	4.5	40	76.5	4.9	40	67.4	5.3	40	60.9	3.6
11—12	38	77.7	4.0	38	83.1	4.9	38	74.2	4.8	38	65.3	3.5
13—14	38	80.8	3.8	38	88.7	4.3	38	80.0	4.2	38	69.2	3.5
15—16	34	85.7	5.6	36	93.4	6.5	36	87.1	6.2	34	74.7	5.4
17—18	19	85.9	5.1	40	93.7	5.3	40	88.4	4.4	23	76.3	4.9
19—20	3	83.7	—	36	94.1	5.3	36	89.1	5.3	8	79.3	—
Girls												
1— 2	39	43.3	5.8	39	33.4	7.6	39	25.5	5.0	39	35.4	5.6
3— 4	29	54.4	3.1	29	52.0	4.4	29	40.3	5.3	29	44.5	2.7
5— 6	25	60.4	3.3	25	61.1	3.8	25	51.6	4.3	25	49.3	2.7
7— 8	27	64.2	3.8	27	66.8	4.7	27	58.2	4.3	27	52.7	3.4
9—10	36	69.6	4.3	36	74.4	4.7	36	65.8	4.1	36	58.1	3.8
11—12	35	74.9	3.7	35	81.0	4.3	35	73.7	4.5	35	64.3	3.9
13—14	35	76.0	2.5	36	83.6	5.0	36	77.6	5.1	35	66.0	5.0
15—16	20	76.3	4.7	33	83.7	4.9	33	77.9	4.6	20	67.2	4.9
17—18	7	80.4	—	38	83.8	4.2	38	78.7	3.9	8	70.9	—
19—20	2	78.5	—	38	84.9	4.6	38	79.7	3.9	5	67.4	—

n = number of cases. M = mean value in mm. σ = standard deviation.

projection, the greatest breadth was measured of both the diaphyses and the epiphyses of the femur and the tibia. From the age of sixteen in boys and fourteen in girls, the epiphysis-diaphysis limit could not be seen in occasional cases; the measurements of the diaphyses in these cases are lacking.

The material was analyzed statistically according to the usual methods (cf. MOSSBERG 1948, p. 43—44).

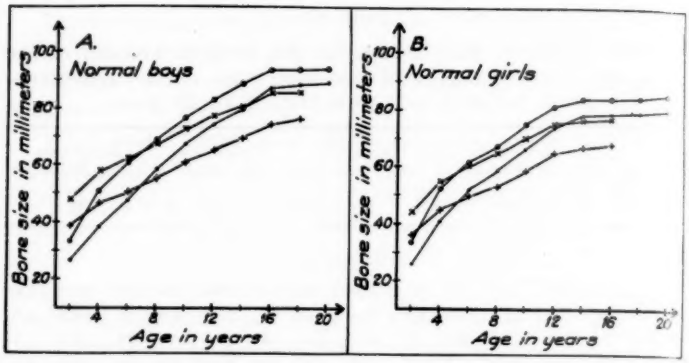

Fig. 1. The greatest breadth of epiphyses and diaphyses of the femur and the tibia in 716 roentgenograms of the knee joints of normal children (380 boys, 336 girls) from 1 to 20 years.

· = epiphysis of the tibia. × = diaphysis of the femur.
+ = diaphysis of the tibia. o = epiphysis of the femur.

Results

The normal mean values obtained are seen in Table 1 and Fig. 1. It appears, as was to be expected, that the breadth of the epiphyses of the femur and the tibia increases more quickly than the breadth of the corresponding diaphyses, and also that the measurements of the epiphyses exceed those of the diaphyses in boys after the age of seven—eight years and in girls after the age of five—six years. The tendency during development is the same in both sexes. The absolute values for the breadth of the epiphyses show, however, that in early childhood the epiphyses of girls grow more quickly and reach higher absolute values than those of boys in the same age groups. After the age of five—six years, on the other hand, the epiphyses of the boys grow more quickly and gradually become larger than those of the girls.

The Knee Bones in Obesity

Material and Methods

The cases on the basis of which x-ray estimations of the knee joint are to be discussed form part of the series of cases of obese children previously described by the author in Acta paediat., *35*,

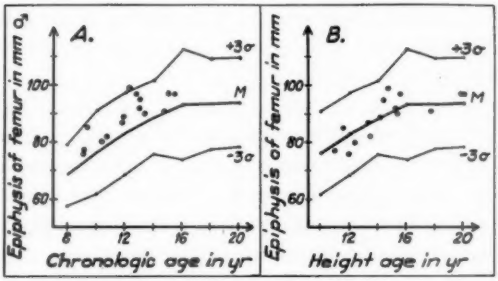

Fig. 2. The greatest breadth of distal epiphyses of the femur in 15 obese overgrown boys versus A: chronological age, B: height age.

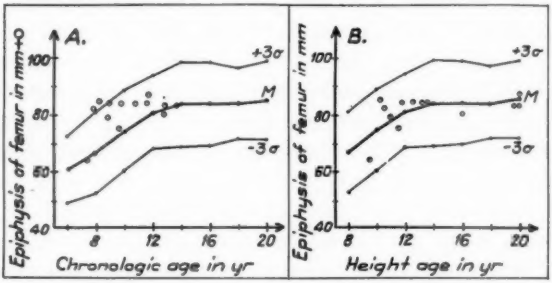

Fig. 3. The greatest breadth of distal epiphyses of the femur in 13 obese overgrown girls versus A: chronological age, B: height age.

Suppl. II, 1948. The material has been restricted to those cases in which the stature was most in advance of the normal height for the age and in which the knee bones were x-rayed.

Fifteen boys and thirteen girls showing obesity and overgrowth are thus included. The stature of the boys was nine to eighteen cm and of the girls ten to twenty and one half cm above the normal mean values for their ages according to the height tables of BROMAN, DAHLBERG, & LICHTENSTEIN. Expressed in multiples of the normal distribution (σ), the corresponding values of these boys were $+1.3$ to $+2.5\ \sigma$ and of these girls $+1.5$ to $+3.2\,\sigma$. Thus all the children were considerably above the mean values for their ages and form a group of children with »gigan-

tism». The age of the boys was $9\,^{1}/_{12}$ to $15\,^{5}/_{12}$ years (mean value $= 12\,^{1}/_{12}$ years) and that of the girls $7\,^{5}/_{12}$ to $13\,^{10}/_{12}$ years (mean value $= 10\,^{4}/_{12}$ years).

As appeared from the description of the normal knee joints, the measurements of the epiphyses of femur and tibia are larger than the corresponding measurements of the diaphyses in boys after seven—eight years of age and in girls after five—six years of age. At the ages which are represented in these cases of obesity and overgrowth, the measurements of the epiphyses would be expected to be larger than the measurements of the diaphyses, since all the cases occur above these critical ages. Furthermore, the limit epiphysis-diaphysis sometimes cannot be distinguished after the age of fourteen to sixteen years. The measurements of the epiphyses, therefore, are related to the corresponding normal values. A comparison has also been made between the chronological age of these obese children and their height age, so that from the height tables an estimate of physiological age is obtained on the basis of which comparison with normal children may be made.

Results

The measurements of the epiphyses of the femur and the epiphysis of the tibia in these cases give comparable results when compared with the normal values. The plotted values of the epiphysis of the femur of the boys are seen in Fig. 2 and those of the girls in Fig. 3.

The diagrams show that most of the *measurements of the epiphysis in relation to the chronological age* are larger than the normal values, in agreement with the opinion of CZERNY and KELLER. When the physically advanced development of the obese children is taken into consideration by assessment of *the physiological age,* another result is obtained. The plotted values of the epiphysis are then grouped around the normal mean value with but trivial deviation upward or downward. This shows that the knee bones in the obese children are not more developed than one would expect from their general early bodily development. The opinion of CZERNY and KELLER that the skeleton in obese over-

grown children is abnormally large in a physiological sense is therefore without support.

Summary

The skeleton in obese overgrown children is said by CZERNY and KELLER to be abnormally well developed. However, the overall early development of obese children has not been taken into consideration. By comparison with statistically-treated normal material the author shows that the knee skeleton of obese children corresponds well with their overall early bodily development. Therefore there is no reason to emphasize the marked skeletal development of large fat children as something deserving attention.

Résumé

Le squelette des enfants obèses et de grande taille a été décrit par Czerny et Keller comme anormalement développé. Cependant, le développement avant tout précoce des enfants obèses ne doit pas être pris en considération. Une comparaison avec un matériel normal étudié statistiquement nous montre, d'après l'auteur, que le squelette du genou des enfants obèses correspond bien à leur développement corporel, avant tout précoce. C'est pourquoi il n'y a pas de raison de mettre l'accent sur le grand développement squelettique des enfants gras, comme sur un fait digne d'attention.

Zusammenfassung

Das Knochengerüst ist bei Kindern mit Adiposo-Gigantismus, nach Angabe von Czerny und Keller abnorm stark entwickelt. Dennoch wurde die im allgemeinen frühe Entwicklung fetter Kinder nicht in Betracht gezogen. Durch den Vergleich mit statistisch bearbeitetem, normalem Material zeigt der Verfasser, dass das Knochengerüst von fetten Kindern ihrer im allgemeinen frühen körperlichen Entwicklung wohl entspricht. Daher besteht hier kein Anlass, die starke Entwicklung des Knochengerüstes bei Adiposo-Gigantismus im Kindesalter als etwas besonders Bemerkenswertes zu betonen.

Sumario

Czerny y Keller opinan que el esqueleto de los niños obesos y de talla excesiva se encuentra anormalmente bien desarrollado. No se ha tenido en cuenta en estos niños obesos, el desarrollo precoz general. El autor muestra en un estudio estadístico cómparativo de material normal, que el esqueleto de la rodilla en los niños obesos, esta de acuerdo con su desarrollo precoz general somatico. Por eso no existe ninguna razón para considerar el buen desarrollo esqueletico de estos niños grandes y obesos, como algo que merezca atención especial.

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FROM THE PAEDIATRIC CLINIC OF KAROLINSKA INSTITUTET AT THE NORRTULL HOSPITAL.
CHIEF: PROF. A. WALLGREN.

How a Child Guidance Clinic Works

by

ELSA-BRITA NORDLUND

In these days the material from a child guidance clinic is a particularly good indication of the different views about child care which now exist in our country. As extreme tendencies are opposing each other, this situation emphasizes the need for helping parents who lack confidence. One often wishes that those people who spread irresponsible propaganda on bringing up children through the press and on the radio would also serve for a very short time in a child guidance clinic and thus be forced to record the effects, for good or ill, of their child care propaganda; they would certainly soon moderate their activities. When such an explosive question as problems of upbringing is involved, it is necessary to establish personal contact, in private interviews, with one's clientele; one must learn to know the people who are to be advised and the children to whom the advice will be applied. Otherwise things will go from bad to worse. A child guidance clinic must therefore be run with a very great sense of responsibility and a friendly and positive attitude on the part of the whole staff towards those seeking help. All social tutelage must be eliminated. One must follow the aphorism coined in America that there is no mother so bad that she has nothing to teach the child psychiatrist. Sympathy and understanding for the clients' real difficulties cannot be too great; understanding contributes to the finding of adequate short cuts which are not a waste of time. The myth of the hysterical mother who is the source of all the child's difficulties must be eradicated and its place taken by a proper analysis of the emotional interplay between mother

and child, an analysis of the unconscious forces which direct the mother's attitude vis-à-vis the child. The child guidance clinic does not aim at bringing up parents; it tries to establish good co-operation between the clinic and parents, not attempt tutelage.

The staff of a child guidance clinic consists of doctors, social workers, psychologists, play-therapists, and typists, and the work is assigned in the following way. When the case is referred to the clinic the mother visits the social worker, who makes a detailed social-medical-psychological case history. There is often an arrangement whereby certain subjects are left to the doctor, however. If there are difficulties at school, or if there is a suspicion of a deficiency in general intelligence, the child is tested by the psychologist before attending the doctor, and in clear-cut emotional problems play in the sand box under observation of the play-therapist is carried out. Then the child and mother are presented to the doctor for the first consultation. This consultation is expected to take two hours, one hour with the mother and one with the child. Children over two years are not present during the interview with the mother, but are taken care of by a nurse who attempts to observe them a little while they are waiting. At the first interview the doctor should play an extremely passive role and should not take up any attitude to the problem except en passant. After the interview with the mother the father is also, if possible, invited to a consultation. In parenthesis it may be said that the fathers are generally very willing to come and are very interested. At the first visit to the doctor a physical examination is usually made unless there is some psychological contraindication, or unless the child has recently had a thorough examination by another doctor. When the case has passed through these stages, the facts are assembled and discussed by the work team at a conference at which all the week's cases come up for discussion. All those who have had contact with the parents and child may put forward their points of view, after which we make a decision on the future steps which should be taken. These may, for instance, include 1) continued interviews with the mother only — this applies especially if the child is very young; 2) talks with the mother and the child, in which a social

worker may perhaps take the mother and the doctor or play-therapist the child for interviews or play-therapy — this applies to the somewhat older children; 3) talks with the child only, sometimes interspersed with interviews with one of the parents to check the effect of the psychological treatment on the child — this applies to older children; 4) change of environment for a short or long period.

A child guidance clinic should be closely connected with a children's hospital for several reasons. One is that all the examinations which must be undertaken in the investigation of a case should be made in the vicinity. These include a thorough clinical examination, roentgenography, encephalography, electroencephalography, ear and eye examinations, etc. Furthermore, since the child guidance clinic's whole staff comes in contact with somatic cases of various types, the approach to the problem can never be one-sided. The new psychosomatic science has helped to build a definite bridge between psyche and soma and enrich both fields of work. Isolated work in a child guidance clinic without daily contact with physically ill children and colleagues concerned with organic disease would be a great loss. Another advantage of a children's hospital is that the clientele go there voluntarily, a circumstance which gives a better milieu, especially from the point of view of contact. The case is otherwise with social institutions, to which the clientele is often referred.

To avoid becoming a sorting station, a child guidance clinic is always supplemented by the possibility of outpatient treatment. The doctor who works merely as an advisor, isolated among the parents and children visiting him, is often possessed by an exaggerated and fixed belief in the constitution as the only decisive factor, whereas the doctor who also carries out treatment and can see something of the dynamics of the psychic characteristics in various age groups acquires a more balanced attitude to the significance of both constitution and environment, a more optimistic and less fatalistic attitude to problems of child care, an optimism that is based not on wishful thinking but on realities experienced in treating children.

Different Attitudes of Parents. — To give some glimpse of the inside of a child guidance clinic at work, I shall outline the various attitudes towards advice shown by the parents.

1) Some parents are referred from schools or social institutions where no clear problem has yet crystallized. The problem lies in some way outside of these persons, and often those seeking help hardly grasp the fact that there is a problem. Here it is difficult to get to the heart of the matter and to avoid making these cases more difficult by too great activity on the part of the investigator. *The fact of having been referred and the lack of any inner need for help makes initial contact more difficult.* This is a category of mothers difficult to help. The group is particularly large when the child guidance clinic is connected with a social institution and the social workers send patients to the former before taking the trouble to explain clearly to the clientele why they have been referred.

2) Those mothers who come because the clinic has been recommended by other mothers or relatives who feel that they themselves have benefited constitute a second category. In these cases also there is often no inner need; they come because other people said they should do so or to satisfy relatives. Here the need is only passive and there is no clear realization of the problem.

3) A third group includes the intellectual mothers who are very interested in child psychology, attend discussion circles, read answers to questions on bringing up children in the newspapers, and willingly discuss these matters. Often they come not to get help, but to ventilate their opinions on the subject and show off their knowledge. At these interviews there may be a really extensive, purely intellectual exchange of views, but from such discussions it is very difficult to get at any real need for help. This does not necessarily exist when they do not seek help in any true sense of the word.

4) We have the psychically tired mothers who dare not or cannot take responsibility, especially not at the moment when the question of upbringing is so confused. They want answers to questions; they often come with a long list of questions to which they want answers. This may spring from a general lack of con-

fidence, but often this attitude is based on true psychic fatigue; to take responsibility is beyond them. Or there are the compulsive neurotic pedants, those with great faith in authority, narrow-minded people who want system in everything, who are in agony if anything does not go according to their ideas. They are not mature enough to deal with the problem of upbringing, which, especially now, calls for enormous adaptability and ability to improvise, above all in the capricious situations which arise in the relations between children and adults. They are not masters of the situation and from the doctor they want answers to a miscellany of questions, answers which will enable them to systematize something which never can be dealt with according to a certain system. To this category belong many women who work outside the home and are used to systematizing things, not to working with living beings.

The last-named category of mothers increases proportionately as the child care situation becomes more chaotic. Then we have those cases where the upbringing problem is a camouflage, more or less conscious, that covers, for instance, a complicated marriage problem which the parents dare not face directly. Finally we have the large category of mothers who have *a real need of help,* who come to us distressed and unable to deal with the child care situation. They have had advice from right and left, they have read leaflets from the child welfare clinic, but nothing has helped. They know, perhaps, how children should be brought up, but they cannot follow the advice given. Every time they have asked for help they have been given advice, but the advice has confused the situation further, because although they feel that the advice given is self-evident, they are, at the same time, incapable of following it. It is something mysteriously inexplicable. This is the case with all the mothers whose methods of rearing children are dictated by unconscious forces of which they are not masters, and which, time and time again, show themselves to be strong enough to paralyze their attempts at bringing their children up in the right way. These mothers are, perhaps, the most satisfying clientele we have, because their helplessness is so great. When we begin together to investigate their unconscious motives by enquiring

into their own childhood and adolescence, much comes out that explains and illuminates their methods of upbringing, methods which even from their own point of view are inadequate, and direct advice often becomes unnecessary.

It is not, however, only the mother's attitude we are interested in; the father's approach to the problem must also be discovered, for which reason we call in the fathers, in so far as it is possible, to get their attitudes to the question of upbringing and form some idea of what it is that determines their approach to the problem. It is important to know these various attitudes so that we know how the problem will be attacked, and where the real need for help lies. It is, however, dangerous to divide people up according to the attitudes they adopt in a certain situation. Yet it is important for oneself to make such a distinction, to ask oneself: what was the motive behind this visit, what does the mother really want from this visit?

Plenty of time must always be allowed for the interview. Let the mother herself direct the conversation and do not, by incessant questions, alter the course of the discussion and face the mother with new problems to which she has not had time to take up a point of view. If she is allowed to talk we can get an idea of what she herself, from her point of view, considers the most important subject. The problem acquires its correct proportions. One must, however, be quite conscious that most mothers who seek advice from the clinic are prepared for criticism from the doctor, which they often try to eliminate prophylactically as soon as the consultation begins by saying: »Yes, it is I who am the problem, it is my fault.» It always happens. When a mother is asked to describe what sort of mother she is, the answer is: »I am rather nervous, and I have a quick temper» and, as one mother added: »It is of course a crime in these days to have a quick temper.» This feeling of being criticized by the doctor directs the conversation to a very large extent, but it is none the less important that the mother's attitude to criticism find expression. When through questions and encouragement she comes to understand that it is not the doctor's object to criticize the parents, but to help them, she really begins to bring the problem into the open. It is in-

structive, after the first conversation, to write down one's impressions of it; these will also interpret the essentials of the interview. Then, after the next meeting with the same mother, the examiner should write another impression, compare these two records, and then consider how wrongly this mother and her problem would have been judged if the case had been discontinued after the first interview. If one is ambitious to achieve quality rather than quantity, and not to make bad into worse, one must have a proper amount of time at one's disposal. Indeed, the more one works in a child guidance clinic, the more careful one becomes about giving advice, and the more one allows the clientele to talk and talk. When the mother finds herself in another person's sphere of sentiment it is as if the problems solved themselves while she talks. She finds the answers herself when she is forced to discuss matters thoroughly with the doctor. In this way she can feel that the advice which is crystallized during the course of the conversation is not a sort of foreign body which must be applied, in accordance with or against her wishes, in a given situation, but that it is something individual, something that grew organically out of herself, and has therefore so much the greater effective power. Here, perhaps, someone will protest that the mothers would never stop talking if they were not checked; but it is good for these mothers to be allowed to talk at twenty miles an hour so as to let them realize the senselessness of it all. They hesitate suddenly, when they are not interrupted, and pounce upon something essential. The exchanges between doctor and mother are a therapeutic factor very peculiar in their nuances and effects, something which one must recognize, and which must curb the doctor's activity and sharpen his sensitivity. One often notices how people need to give expression to their aggressions, to run down husband and child, teachers and landladies, before they can get started on the path that leads to the real problem. It is important that their aggressions are not obstructed here. If that is done the mothers may often feel that the doctor is in collusion with the person at whom the aggression is aimed. Many believe that if one takes up a passive attitude during these outbreaks of aggression, the mothers interpret this as meaning that the doctor

is on their side and accepts the justice of the aggression. The feeling that the doctor is on the patient's side is, however, only a favourable factor which will help the doctor to gain his objective view of the situation.

Finally I come to the principle embodied in our more active advising. We have no standardized advice, but in principle attempt the following: we try through our conversation to strengthen the mothers' self-esteem and to teach them to take every child in an unprejudiced way. We emphasize that every child has his own environment, even if several children have the same parents and grow up in the same house. We try to impress upon them that there is no standardized scheme for bringing up children which can be drawn up in advance. A method of bringing up a child must grow parallel with the knowledge of the child that is to be reared. We point out the significance of the emotional anchoring where a child's behaviour pattern is concerned. We try to stress that one should not concentrate on *bringing up* a child just for the time when it is in a state of physiological adaptation which causes initial disturbances in behaviour which in their turn easily provoke a too active interference from those who look after the child. We try to make the mothers understand that the younger the child is, the more important it is that the emotional contact be good, to enable us to make demands of the child. We try to point out that there must be both freedom and constraint in upbringing, but freedom must not be confused with lack of responsibility, supervision, and care, and constraint must not consist of meaningless demands. We also decide on the basis of the intelligence test where the upper boundary of the child's intellectual capacity lies; we must learn this in order to understand the demands made on him, even if in spite of it we are often forced to make demands that the child does not understand.

Finally, we do everything to avoid binding the parents to the child guidance clinic and thus increasing their psychic laziness of thought. This could be one of the disadvantages of a child guidance clinic. We want to help parents to help themselves, which is best done by accentuating the great importance of individual upbringing.

Summary

The author tells how a child guidance clinic connected with a hospital (the Norrtull Hospital, Stockholm) functions.

Résumé

L'auteur nous explique comment fonctionne une Clinique de Neuro-Psychiatrie Infantile au sein d'un Hôpital (Hôpital Norrtull, Stockholm).

Zusammenfassung

Die Verfasserin berichtet, wie eine Kinderfürsorge-Klinik arbeitet, die an ein Krankenhaus angeschlossen ist (Norrtull Krankenhaus, Stockholm).

Sumario

El autor nos relata como funciona una clinica de higiene mental del niño conectado a un hospital de niños (Hospital Norrtull de Estocolmo).

FROM THE PAEDIATRIC DEPARTMENT OF THE RIGSHOSPITAL, COPENHAGEN.

The Prothrombin Content of the Blood During the First Years of Life[1]

by

P. PLUM

The first observations on prolonged coagulation time in newborn children suffering from haemorrhagic diathesis were reported in 1912 by WHIPPLE (23) and in 1920 by RODDA (17). SALOMONSEN (18) studied the coagulation time in a large number of newborn infants both with and without haemorrhages and found that it was prolonged during the first days of life, especially in children with haemorrhages. The first study of prothrombin in newborn infants was made in 1937 by BRINKHOUS, SMITH, and WARNER (1), who found that the prothrombin content of the blood in normal newborn infants was only half that in adults. Two years later independent investigations revealed that haemorrhagic diathesis in newborn infants is due to lack of vitamin K and that the disease may be cured and prevented by this vitamin (20, 12, 6, 10, 3).

Since then numerous reports have confirmed and elaborated these observations. Suffice it to say that in normal infants the prothrombin content of the blood at birth is somewhat lower than in older children and adults; it decreases during the following two-four days and subsequently increases from about the fourth day, slowly approaching the normal adult values.

In the following are reported the results of investigations carried out on one thousand normal newborn infants and one hundred and eighty normal children up to the age of twenty one months.

[1] With the support of the Rockefeller Foundation.

I. Normal Newborn Infants

Method. For the determination of the prothrombin content of the blood QUICK's (16) method was used as modified by LARSEN and PLUM (9). The determinations were made at a temperature of 37° C. 0.1 cc blood was taken from a freely bleeding puncture in the heel into a pipette containing 0.2 cc of a 0.3 % sodium citrate solution in 0.78 % NaCl. The blood-citrate mixture was quickly placed in a small pointed test tube which was then set in a water bath; to this was added one drop of a thromboplastin preparation (DAM and GLAVIND, 2) and lastly 0.025 cc 1 % $CaCl_2$, 2 H_2O. The coagulation time was measured with a stop watch; for normal adults it was seventeen—nineteen seconds. The extent to which the findings are reproducible has been reported in an earlier paper.

Material. Three thousand determinations were made on one thousand normal newborn infants. Neither the children nor their mothers had been given vitamin K. Each of the children was examined three times, most of them on the first day after birth, the fourth day, and the seventh or eighth day. Some, however, were examined on the intervening days. The investigations were carried out in the Maternity Department of the Rigshospital in Copenhagen during the course of one year. The majority were breast-fed, but a smaller number of artificially-fed children was also included.

The total number of prothrombin values is shown in Fig. 1. It will be seen that on the first day there is a great accumulation of prothrombin values between 20 % and 40 %; only a few hours after birth, however, several children have far lower values (the unit taken in recording these values was one hour). During the second and third days the values vary considerably more and it will be seen that the average level has decreased to between 5 % and 20 %. During the fourth day there is a considerable variation, with many very low values, but the average level has begun to increase. This increase becomes more pronounced on the fifth day and still more on the seventh and eighth days, where the ma-

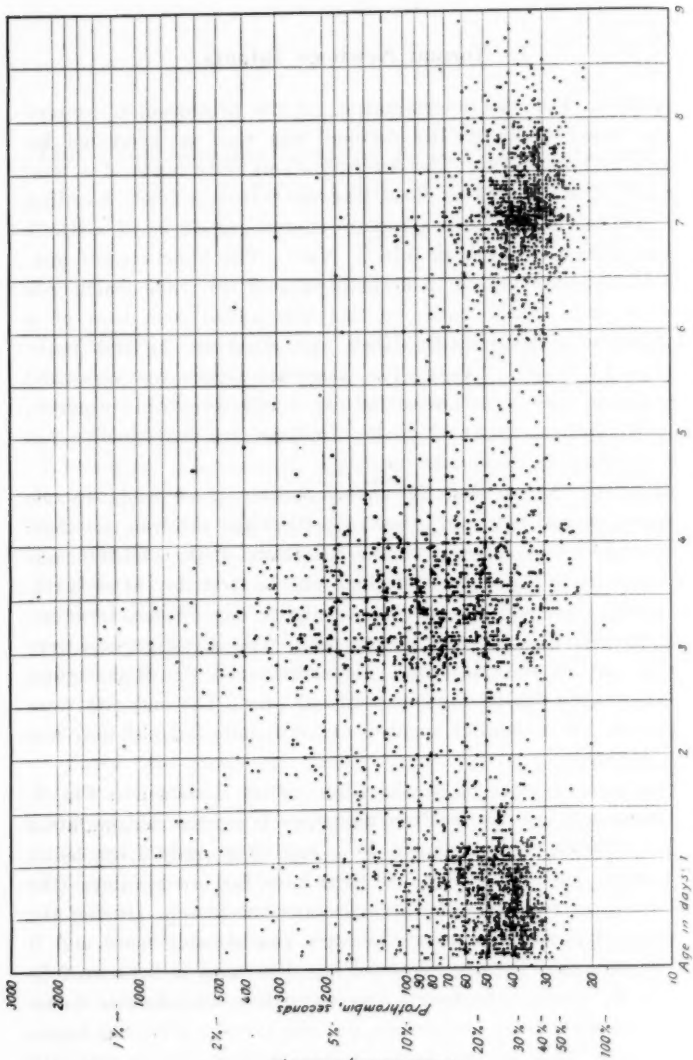

Fig. 1. 3 000 prothrombin tests on 1 000 infants during first 9 days after birth.

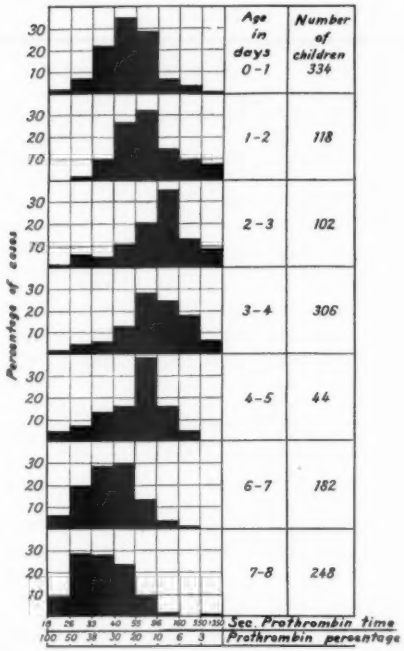

Fig. 2. Distribution of prothrombin values on each of first 8 days after birth.

jority lie a little higher than on the first day, namely between 25 % and 50 % of the normal adult value.

The distribution of the prothrombin values over the first eight days of life is shown in Fig. 2. As will be seen, up to the third day the vertex gradually moves towards lower values and then begins to rise slowly. On the seventh to eighth day more than half of the children still have a prothrombin content of the blood which is less than 50 % of the normal adult value.

The possible seasonal variation of the prothrombin values has been considered (Table 1 and Fig. 3). The material has been tabulated under three age groups and for each group the distribution within the various ranges of prothrombin values has been

Table 1.

Time After Birth	Month	Prothrombin Time, Sec. 18–26	27–33	34–40	41–55	56–96	97–160	161–350	>350	Numbers of Children
		Prothrombin Percentage 100–50	50–38	38–30	30–20	20–10	10–6	6–3	<3	
		%	%	%	%	%	%	%	%	
0—24 Hours	May—June ..	2.8	7.1	21.4	34.5	26.2	5.9	2.4	0	84
	July—Aug. ..	3.1	7.2	27.8	28.9	23.7	4.1	4.1	1.0	97
	Sept.—Oct. ..	0	7.4	13.7	37.9	29.5	6.3	4.2	1.1	95
	Nov.—Dec. ..	1.0	6.3	21.9	34.4	26.1	6.3	4.2	0	96
	Jan.—Feb....	1.0	9.6	25.0	30.8	25.0	8.7	0	0	104
	March—April.	0.6	7.8	23.3	28.3	26.1	6.7	3.9	3.3	180
	Average	1.42	7.57	22.20	35.50	26.10	6.33	3.31	0.90	
2—3 $^{23}/_{24}$ Days	May—June ..	0.9	4.6	6.5	11.1	29.6	26.8	15.7	4.6	108
	July—Aug. ..	0.9	4.3	6.0	11.2	23.3	27.6	19.0	6.0	116
	Sept.—Oct. ..	3.9	6.0	4.3	12.9	26.7	26.7	14.6	5.2	116
	Nov.—Dec. ..	0.8	2.4	4.2	14.4	28.0	28.8	13.6	7.6	118
	Jan.—Feb. ..	2.4	4.1	1.6	21.1	31.7	19.5	17.9	1.6	123
	March—April.	1.8	5.0	8.3	10.1	32.6	21.1	16.5	4.6	218
	Average	1.85	4.40	5.15	13.60	28.60	25.10	16.20	4.90	
6—7 $^{23}/_{24}$ Days	May—June ..	5.0	24.8	32.0	24.0	12.4	1.7	0	0	121
	July—Aug. ..	12.9	22.6	25.0	26.7	9.7	2.5	0.8	0	124
	Sept.—Oct. ..	5.8	25.6	25.6	26.4	14.1	1.7	0	0.8	121
	Nov.—Dec. ..	8.3	28.7	26.9	25.9	8.3	1.9	0	0	108
	Jan.—Feb. ..	5.6	32.2	28.2	25.8	8.1	0	0	0	124
	March—April.	8.5	29.2	23.1	21.7	13.7	2.8	0	0.47	212
	Average	7.68	27.20	26.82	25.08	11.05	1.78	0.13	0.21	

computed, the year being divided into six periods of two months. As may be seen, no systematic seasonal variation is apparent. Dr. Dyggve, who is continuing these investigations, has found some seasonal variation.

The effect of diet has been studied. However, as only fifty three artificially-fed infants were available, these were compared with the total number of infants, of whom by far the larger number were known to be breast-fed. Table 2 shows that the

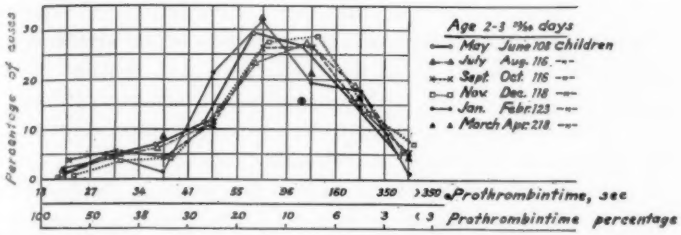

Fig. 3. Distribution of prothrombin values in infants from 2—4 days old examined during 6 consecutive 2-month periods.

artificially-fed infants in the three age groups examined have a considerably higher prothrombin value than the breast-fed infants. Similar results were reported by SALOMONSEN and NYGAARD (19, 11), and by HJALMAR LARSEN (7).

It has been considered further whether there is a correlation between the prothrombin level and the changes in weight during the first week of life, a possibility which beforehand seems likely. HJALMAR LARSEN (7) has demonstrated that the prothrombin content of the blood rises proportionately with the milk consumption of the infant, whether the milk is cow's milk or mother's milk. The children were divided into three groups: one comprising infants who had gained 100 g or more in weight during the first week; one whose weight had not varied more than 50 g above or below the weight at birth; and lastly one group comprising infants who lost more than 100 g during the first week. A total of just over four hundred infants was tested and it was found that the prothrombin level was nearly the same in the three groups.

Table 2.

Age	Prothrombin Less Than 20 %		Prothrombin 20—100 %	
	Nursing Infants	Artificially-Fed Infants	Nursing Infants	Artificially-Fed Infants
0—23 Hours	41 %	24 %	59 %	76 %
2—3 Days	75 %	33 %	25 %	67 %
6—7 Days	13 %	0 %	87 %	100 %

It has been shown (14) that there is no definite correlation between the weight at birth and the variations of the prothrombin during the first week. It has also been shown (14), contrary to expectation, that children with pronounced physiological jaundice are inclined to have a slightly higher prothrombin content of the blood than those with no noticeable jaundice.

I do not intend further to discuss the cause of the low prothrombin level during the first week. It will suffice to mention that the most essential factor is a lack of vitamin K. But it is likely that there is another factor, inasmuch as during the first week infants cannot be made to reach normal adult values of prothrombin in spite of ingestion of large doses of synthetic or natural vitamin K. It must be supposed that the cause is the immature condition of the liver; i.e., the liver of the newborn does not have the same prothrombin-forming capacity as that of the adult.

II. Children From One Week to Twenty One Months

The same method was used as in the newborn.

Material. Two hundred and twenty determinations were made on one hundred and eighty normal children aged from one week

Table 3.

Prothrombin Time Sec.	Age in Months							
	1/2–1	1–3	3–5	5–6	6–9	9–12	12–21	Adults
40.0—54.9	3							
32.0—39.9	17							
26.0—31.9	30							
24.0—25.9	19	11						
22.0—23.9	14	17	7	5		10		
20.0—21.9	14	17	25	20	27	35	4	9
18.0—19.9	3	44	43	35	42	35	42	45
16.0—17.9		11	25	40	31	15	54	36
14.0—15.9						5		10
Number of Children	36	18	28	20	26	20	26	107

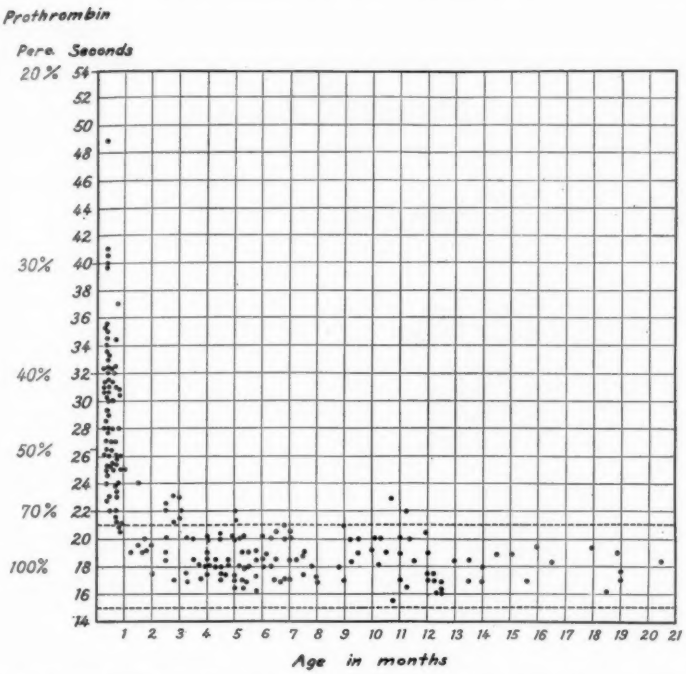

Fig. 4. 220 prothrombin tests on 180 normal children aged from 1 week to 21 months.

to twenty one months (Fig. 4). The children were examined in the Maternity Department of the Rigshospital and in two children's homes in Copenhagen. In addition we examined seventy six children in the Paediatric Department aged from one month to fourteen years and known to be free from diseases which might cause a reduction of the prothrombin content of the blood. The results are given in Table 3 and in Figs. 4 and 5. It will be seen that during the second half of the first month the prothrombin is still at a considerably lower level than in adults, while during the second and third months after birth the distribution is approaching that of normal adults, but still from the third to the sixth month and from the sixth month to the twelvth month there

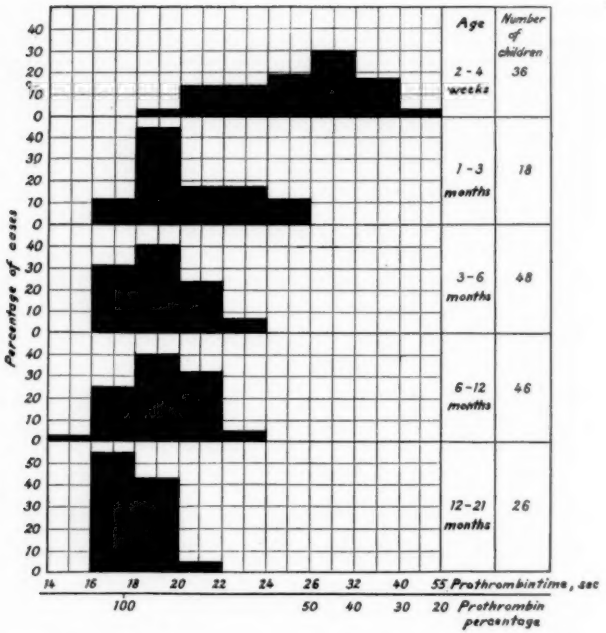

Fig. 5. Distribution of prothrombin values expressed in percentage. Various age groups within the first 21 months.

are lower prothrombin values than in older children and adults. While the tests on smaller children have been made with blood taken from the heel, the tests on older children and adults have been made with blood taken by venous puncture, in order to make possible a greater number of determinations for each test.

WARNER, BRINKHOUSE, and SMITH (1), examining eleven normal children, found a gradual rise in the prothrombin values from the age of one month to one year. The tests were made by the two-stage method described by the same authors (21). At the age of about two months they found values about 60 % of the normal adult value. Thereafter the prothrombin rose slowly to 100 % at the end of the first year.

Summary

1. The variations in the prothrombin content of the blood have been examined in one thousand normal infants.

2. No seasonal variation in the prothrombin content of the blood of the newborn was found. The prothrombin level of artificially-fed infants is considerably higher during the first week of life than that of nursing infants. No certain correlation between the prothrombin content of the blood and the changes in body weight during the first week was found.

3. The prothrombin content of the blood during the first twenty one months has been examined in one hundred and eighty normal children. From the age of three months the greater number of children examined lie within the normal range for older children and adults. It is not until the age of one year that the prothrombin content is the same as that of adults.

Résumé

1. Les variations de la teneur du sang en prothrombine ont été étudiées chez 1 000 enfants normaux.

2. On n'a pas trouvé de variation saisonnière dans la teneur du sang en prothrombine chez le nouveau né. Le taux de la prothrombine chez les enfants nourris artificiellement est, durant la première semaine après la naissance, considérablement plus élevé que chez les enfants nourris au sein. Il n'a pas été trouvé de corrélation certaine entre la teneur du sang en prothrombine et les variations du poids du corps durant la première semaine.

3. La teneur du sang en prothrombine durant les premiers mois a été examinée chez 180 enfants normaux. A partir de l'âge de trois mois, la plupart des enfants examinés se trouvent être dans les limites de variations normales pour des enfants plus agés et pour des adultes. Ce n'est qu'à partir de l'age d'un an que la teneur du sang en prothrombine est la même chez les enfants que chez les adultes.

Zusammenfassung

1) Die Schwankungen des Prothrombingehaltes im Blute bei 1 000 gesunden Kindern wurden untersucht.

2) Inbezug auf die Jahreszeit wurde kein Unterschied im Prothrombingehalt des Blutes bei Neugeborenen festgestellt. Das Prothrombin-Niveau bei künstlich ernährten Kindern ist in den ersten Lebenswochen bedeutend höher als bei Brustkindern. Es ergab sich keine sichere Relation zwischen dem Prothrombingehalt und den Veränderungen des Körpergewichtes während der ersten Lebenswoche.

3) Der Prothrombingehalt im Blute während des ersten Monats wurde bei 180 gesunden Kindern untersucht. Am dritten Lebensmonat lag der Prothrombingehalt bei der Mehrzahl der Kinder innerhalb der normalen Grenze für ältere Kinder und Erwachsene. Erst bei 1 Jahr ist der Prothrombingehalt der gleiche wie bei Erwachsenen.

Sumario

1) Se ha estudiado las variaciones del contenido de la protrombina en la sangre de 1 000 niños normales.

2) No se ha encontrado variaciones temporarias en el contenido de protrombina de la sangre del recien nacido. La tasa de protrombina en los niños alimentados artificialmente es durante la primera semana después del nacimiento, considerablemente mas elevada, que en los niños alimentados a pecho. No se ha encontrado correlación entre la tasa de protrombina en la sangre y las variaciones del peso corporal durante la primera semana.

3) El contenido de protrombina en la sangre durante los primeros meses ha sido examinado en 180 niños normales. A partir de la edad de tres meses, la mayoria de los niños examinados se encuentran en los limites de las variaciones normales, para los niños de mas edad y para los adultos. Es recien a partir de la edad de un año, que la tasa de protrombina en la sangre es la misma en los niños que en los adultos.

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FROM THE PAEDIATRIC CLINIC OF THE UNIVERSITY OF TURKU.
CHIEF: PROF. T. SALMI, M.D.

Observations on Blood Levels of Penicillin in Premature Infants With Oral Use of the Drug

by

EVA RENKONEN, L.M.

Reports pertaining to the oral administration of penicillin to children are relatively scarce in the literature, nor is there any unanimity as to the method of administration. I have been unable to find in the literature a single instance of research dealing in particular with premature infants.

Penicillin therapy applied per os to young babies has been studied e.g. by REISMAN, GOLDFARB, and MOLLOY (1947); MARKOWITZ and KUTTNER (1947); HUSSON (1947); and COHLAN, LEWIS, and SELIGMANN (1948).

In order to increase the blood levels of penicillin when administering it by the mouth, several methods have been tested. These include:

1. protection of penicillin from the hydrochloric acid in the gastric juice by:
   a) buffers,
   b) administration in capsule form, and
   c) administration in oil;
2. use of a more repository penicillin; and
3. over-dosage of penicillin.

REISMAN AND ASSOCIATES have used for infants massive doses of penicillin (50 000—100 000 units) buffered with aluminium hydroxide, calcium carbonate, and magnesium oxide. Their material comprised 22 cases. The results were discouraging. In 2 patients only did the penicillin titer rise to 1 Oxford unit per 1 ccm, while in 6 the titer rose above 0.03 units/ccm and in 15 penicillin could not be demonstrated in the blood at all.

REISMAN AND ASSOCIATES have also done research on the most suitable moment for penicillin administration in relation to meals. They came to the conclusion that it is most advantageous to give the drug either half an hour before or 3 hours after the meal, when a sufficient penicillin titer can be maintained for about $1\,^1/_2$ hours. Their tests did not reveal any difference between ordinary and buffered penicillin.

MARKOWITZ and KUTTNER have also studied the effect of meals on the blood levels of penicillin. No significant difference was found when administering the drug either 1 hour before or immediately before the meal, although somewhat higher values were obtained in the first group. They also found that the penicillin titer of one and the same subject could vary greatly from day to day. When administering penicillin after the meal (in 2 immediately after and in 15 $2\,^1/_2$ hours after the meal), effective penicillin quantities could not be attained in the blood, with one single exception. In conformity with earlier workers, they also used massive doses (50 000 units) of penicillin.

HUSSON made determinations of penicillin contents in the blood of young babies by giving doses of 20 000 units; the highest values were found half an hour after administration (averaging 0.880 units). Samples taken in 4 hours revealed that the titer had decreased on an average to 0.045 units. His material embraced a total of 22 infants (from 1 week to 5 months old). HUSSON is of the opinion that the high penicillin titer values obtained in infants are due to 3 main factors: the low hydrochloric acid titer in the gastric juice, the poor excreting ability of the kidneys, and the small penicillinase formations in the alimentary canal of young infants.

COHLAN AND ASSOCIATES also investigated the blood levels of penicillin, using on the one hand an ordinary and on the other a buffered penicillin solution. A distinct difference between the two could be noted in children 2—12 years old, higher values having been obtained with buffered than with ordinary penicillin, whereas this difference was not clearly visible in infants from 1 week to 4 months old. They used doses of 3 000—5 000 units per kg.

Table 1

Nos.	1	2	3	4	5	6	7	8
Birth Weight (g)	2015	2250	1980	2015	2250	2500	2450	2450
Weight (g)	1860	2800	2220	1800	2850	2825	3000	3000
Age (Days)	31	96	14	32	96	57	90	90
Penic. Dose	10 000	10 000	10 000	10 000	10 000	5000	5000	5000
Time (Min.):								
Meal → Penic.	75	60	30	45	180	135	150	150
Penic. → Meal	45	120	90	75	15	45	75	75
Penic. → Blood-Sample	120	120	120	120	120	60	60	180
Meal → Sample of Gastric Juice	60	45	—	—	—	—	100	100
pH of Gastric Juice	4.9	5.6	—	—	—	—	3.9	3.9
Penic. Titer	0.125	0.06	0.125	0.06	0.250	0.5	0.250	0.015

Nos.	21	22	23	24	25	26	27	28
Birth Weight (g)	1920	1850	1850	1850	1850	2200	2200	2110
Weight	1800	1700	1700	1820	1820	2360	2360	2050
Age (Days)	12	26	26	27	27	32	32	32
Penic. Dose	4000	4000	4000	5000	5000	5000	5000	5000
Time (Min.):								
Meal → Penic.	90	90	90	90	90	30	30	30
Penic. → Meal	30	30	30	30	30	150	150	150
Penic. → Blood-Sample	150	60	150	60	150	60	150	60
Meal → Sample of Gastric Juice	—	90	90	90	90	30	30	30
pH of Gastric Juice	—	3.8	3.8	4.5	4.5	5.5	5.5	5.7
Penic. Titer	0.06	0.125	0.125	0.125	0.125	0.06	<0.06	0.06

Nos.	41	42	43	44	45	46	47	48
Birth Weight (g)	1850	1850	1650	1650	1507	1507	1650	1650
Weight (g)	2350	2350	2040	2040	2220	2220	2110	2110
Age (Days)	55	55	62	62	91	91	66	66
Penic. Dose	5000	5000	5000	5000	5000	5000	5000	5000
Time (Min.):								
Meal → Penic.	30	30	30	30	30	30	30	30
Penic. → Meal	150	150	150	150	150	150	150	150
Penic. → Blood-Sample	60	150	60	150	60	150	60	150
Meal → Sample of Gastric Juice	30	30	30	30	—	—	—	—
pH of Gastric Juice	—	—	5.6	5.6	—	—	—	—
Penic. Titer	0.06	0.125	0.250	0.125	0.250	0.125	0.250	0.125

1

9	10	11	12	13	14	15	16	17	18	19	20
1507	1507	2400	2400	1850	1850	2200	2200	2200	2200	2110	1920
1560	1560	2140	2140	1780	1780	2000	2000	2200	2200	2020	1800
23	23	27	27	20	20	14	14	23	23	25	12
5000	5000	5000	5000	4000	4000	4000	4000	4000	4000	4000	4000
160	160	60	60	80	80	80	80	90	90	110	90
15	15	90	90	30	30	30	30	30	30	30	30
60	180	60	150	60	150	60	195	60	150	150	60
30	150	50	50	80	80	—	—	90	90	110	90
6.2	4.5	6.2	6.2	5.5	5.5	—	—	3.1	3.1	2.3	—
0.5	0.250	0.125	0.06	0.06	0.03	0.125	0.06	0.125	0.06	0.03	0.06

29	30	31	32	33	34	35	36	37	38	39	40
2110	2000	2000	2000	2000	1950	1850	1850	1850	1850	1880	1880
2050	2430	2430	1880	1880	2680	2260	2260	1860	1860	1710	1710
32	63	63	27	27	79	49	49	35	35	5	5
5000	5000	5000	5000	5000	5000	5000	5000	5000	5000	5000	5000
30	30	30	30	30	30	30	30	30	30	30	30
150	150	150	150	150	150	150	150	90	90	90	90
150	60	150	60	150	60	60	150	60	150	60	150
30	30	30	30	30	30	30	30	30	30	30	30
5.7	6.3	6.3	5.7	5.7	5.2	6.5	6.5	5.9	5.9	6.0	6.0
<0,06	0.125	0.125	0.250	0.250	0.03	0.06	0.125	0.5	0.250	0.5	0.5

The research work referred to above seems to indicate that administration of penicillin to infants by mouth would probably be successful in small doses without recurrence to special preparations. In addition to HUSSON's 3 promoting factors, mention might be made of hyperaemia in the ventricular walls; BILLARD (1839) was the first to ascertain that this was characteristic of newborn premature babies and the circumstance was made use of e.g. by YLPPÖ when administering oxygen to asphyxiated premature and newborn infants. The effect of meals could be expected to constitute a drawback, since the premature have to be fed oftener than other young infants.

My material comprises 18 premature babies in whom a total of 48 penicillin determinations was made. The penicillin determinations in the blood were carried out according to RAMMELKAMP's method.[1, 2]

The results are given in Table 1.

A study of the table yields the following observations.

1. Although penicillin per os is administered to prematures in comparatively small doses (4 000—10 000), in several cases the penicillin blood contents were induced to rise above the value regarded as a therapeutic minimum (0.06 units/ccm). This is illustrated by the following summary:

Time Between Penicillin Administration and Taking of Blood Specimen	Penicillin Titer of Blood						Cases
	0.5	0.250	0.125	0.06	0.03	< 0.03	
0—1 hr.	4	5	6	6	1	—	22
1—2 »	—	1	2	2	—	—	5
2—3 »	1	3	8	4	4	1	21
Total	5	9	16	12	5	1	48

[1] An interpretation of the results was rendered difficult by the chylus contents and hemolysis in the samples; these are more common in the blood specimens of prematures than in others. Owing to these reasons an assessment of the results often presented great difficulties.

[2] I have performed the laboratory research at the Sero-Bacteriological Institute of the University of Turku, to the director of which, Professor EERO MUSTAKALLIO, I wish to express my best thanks for his valuable assistance.

As shown by the above synopsis, a sufficient penicillin titer (minimum 0.06 units/ccm) was found:

within 1 hour 21 times in 22 examined specimens
» 2 hours 5 » » 5 » »
» 3 » 16 » » 21 » »

From these observations the conclusion can be drawn that penicillin administration to premature infants per os is an effective method when fairly small doses are used. A sufficient penicillin titer could be found in nearly 100 % of blood samples taken in 1 and 2 hours, and still in about $^3/_4$ of the samples taken in 3 hours.

2. The penicillin titer of the blood varies greatly in different observations.

This phenomenon has been substantiated by earlier investigators as well. Several reasons can be assumed for it, above all the following:

1. administration with regard to meals,
2. individual variations (age and weight of patient, pH of the gastric juice etc.).

The former factor, administration with regard to meals, has been proved important by previous investigations where infants and older children are concerned, inasmuch as it was found that penicillin therapy best served its purpose when applied on an empty stomach in order to produce as high penicillin blood levels as possible.

In the examination of prematures this circumstance had an interest of its own, since it is known that the feeding of premature babies is different from that of other infants, the meals of the former having to follow closely upon one another, so that the stomach of a premature is practically speaking never empty. It was to be feared on the basis of earlier research that this factor would play a very unfavourable part in the oral administration of penicillin, particularly where premature babies were concerned.

In order to throw light upon this question I have performed a series of experiments in which penicillin was administered at different times with regard to meals. My observations are tabulated below.

Penicillin Administered	Penicillin Titer						Cases
	0.5	0.250	0.125	0.06	0.03	< 0.03	
1. *Penicillin Titer in 1 Hour.*							
½ hr. since meal	2	4	1	4	1	—	12
½—1½ » » »	—	—	2	1	—	—	3
1½ » » »	2	1	3	1	—	—	7
2. *Penicillin Titer in 2—3 Hours.*							
½ hr. since meal	1	2	7	—	2	—	12
½—1½ » » »	—	—	1	4	1	—	6
1½ » » »	—	2	2	2	1	1	8

The number of observations made is fairly small, which implies a risk in drawing any definite conclusions. There seems to be some indication to the effect that the administration of penicillin with regard to meals is of less significance to prematures than to other young and older children. Yet one is inclined to feel that in samples taken in 1 hour somewhat higher penicillin levels may be obtained in such instances where $1\,^1/_2$ hours have elapsed since the meal than in those where penicillin was administered half an hour after the meal. On the other hand, the state of things seems to be reversed in samples taken later. This observation may indicate that penicillin given half an hour after the meal is resorbed more slowly than if administered on an empty stomach. Therefore the effectiveness of penicillin is in a way maintained over a longer period of time, the level being simultaneously lower.

Since it seems, however, that by administering penicillin on an empty stomach a somewhat higher titer is obtained, this form of application should be considered more advantageous, the penicillin doses succeeding each other with sufficient frequency in any case.

In order to elucidate the question of individual variations in the penicillin titer, I have performed a series of experiments in which the pH of the gastric juice was also studied. My observations are illustrated by the following table.

pH	Penicillin Titer						Cases
	0.5	0.250	0.125	0.06	0.03	< 0.03	
	1. *Penicillin Titer in 1 Hour.*						
2—3	—	—	—	—	—	—	—
3.1—4	—	1	2	—	—	—	3
4.1—5	—	—	1	—	—	—	1
5.1—6	2	2	—	3	1	—	8
6.1—7	1	—	2	—	—	—	3
	2. *Penicillin Titer in 2—3 Hours.*						
2—3	—	—	—	—	1	—	1
3.1—4	—	—	1	1	—	1	3
4.1—5	—	1	2	—	—	—	3
5.1—6	1	2	1	1	3	—	8
6.1—7	—	—	2	1	—	—	3

The table shows that notwithstanding fairly considerable pH variations, it is not demonstrable that pH has any effect whatever on the penicillin titer values in each individual case. It must therefore be concluded that the individual variations are due to some other factors.

Some factors which can be assumed to influence the individual fluctuations in the penicillin titer are the weight and age of the premature babies at the time of examination. The variations in weight of the prematures I examined were so small that they could not be expected to yield any measurable difference in the penicillin titer when applying Rammelkamp's method. On the other hand, it can be expected that different age groups, from a few days to a few months old, represent dissimilar physiological conditions, possibly evidenced by the results.

To throw some light upon this matter I present the following table.

Age	Penicillin Titer						Cases
	0.5	0.250	0.125	0.06	0.03	< 0.03	
			1. *Penicillin Titer in 1 Hour.*				
0—14 Days	1	—	1	1	—	—	3
15—28 »	1	1	4	1	—	—	7
>28 »	2	4	1	4	1	—	12
			2. *Penicillin Titer in 2 Hours.*				
0—14 Days	1	—	1	2	—	—	4
15—28 »	—	2	2	2	2	—	8
>28 »	—	2	7	2	2	1	14

The table makes it clear that age as such does not produce any fluctuations in the penicillin titer, since considerable difference is present in all the groups and no titer value is characteristic of any age group.

In order to explain the individual variations one might assume that one and the same subject always reacts to penicillin in approximately the same way, or that the same subject at different times reacts in a different manner. For an elucidation of this circumstance I present the following table illustrating the penicillin titer values obtained in different individuals at different times.

Premature Infant	Penicillin Titer in 1 Hr.			Penicillin Titer in 2 Hrs.		
	1st Det.	2nd Det.	3rd Det.	1st Det.	2nd Det.	3rd Det.
A	—	—	—	0.125	0.06	—
B	0.5	0.250	—	0.250	0.125	—
C	0.125	0.125	0.06	0.06	0.06	0.03
D	—	—	—	0.03	0.03	—
E	0.125	0.125	0.5	0.125	0.125	0.250
F	0.06	0.06	—	0.125	0.125	—
G	0.250	0.250	—	0.125	0.125	—

The table illustrates a very interesting fact. It appears as if each premature baby always had the same type of reaction to penicillin in examinations performed at different times. Some infants always show higher, some always lower titer values. This circumstance has an evident practical significance in the planning of penicillin therapy for each individual, since the dose to be applied must be different in different cases.

Conclusions

In the oral administration of penicillin to premature babies small doses are sufficient to maintain an effective therapeutic blood level of the penicillin titer.

The titer values obtained vary greatly even under similar conditions. This seems to be due to the reaction to penicillin typical of each individual. This reaction is not affected by the age of the premature baby, nor by the pH of the gastric juice.

The administration of penicillin in relation to meals does not seem to have the same significance as in other infants or older children, even if there are some indications that slightly higher penicillin titer values can be attained in prematures as well if the drug is administered on an empty stomach. It appears, on the other hand, that if penicillin is given after a meal, the resorption into the blood is slower. Therefore a somewhat more prolonged, although weaker, effect is achieved.

In consequence of individual variations in the penicillin titer of the blood, it is advisable when administering penicillin therapeutically or prophylactically, to perform in each case some determinations of the penicillin titer in order to expose the manner of reaction of each individual; this would make it possible to increase the dose if necessary or to proceed to parenteral therapy.

Summary

The purpose of this investigation was to study the possibilities of administering penicillin orally to premature infants. The material comprises 18 cases in which the penicillin titer was determined 48 times. It was found that even small doses (4 000—

10 000 units) were able to increase the penicillin titer of the blood to a sufficiently high therapeutic level (= 0.06 or above). The samples taken 1 and 2 hours after administration revealed a sufficient titer in almost all cases, and even after 3 hours in $^3/_4$ of the cases. It appeared that administration before meals led to somewhat higher values, but these values were maintained for shorter periods than when administration occurred after meals. The penicillin titer values obtained in different experiments varied considerably. These variations did not seem to be due to variations in the pH of the gastric juice, nor to variations in the age of the premature infants, but a more important factor appeared to be the individual reaction towards penicillin in each case, since the reaction of each individual varied in approximately the same manner in the different experiments.

On the basis of the results obtained the author has drawn a number of conclusions with respect to the practical planning of penicillin therapy.

Résumé

Le but de l'investigation a été d'étudier les possibilités d'administration de la Pénicilline à des enfants nés avant terme. Le matériel comprend 18 cas dans lesquels on a fait 48 fois le dosage sanguin de la Pénicilline. On a trouvé que de petites doses (4 000—10 000 unités) sont susceptibles d'élever suffisamment (0.06 ou plus) le niveau thérapeutique de la Pénicilline titre dans le sang. Un échantillon, prélevé une ou deux heures avant l'administration, a montré un dosage suffisant dans presque tous les cas, et même après trois heures, dans les $^3/_4$ des cas. Il apparut que l'administration de Pénicilline avant les repas donnait lieu à des valeurs un peu plus élevées, mais celles-ci étaient maintenues pour des durées plus courtes que lorsque l'administration se faisait après les repas. Les valeurs de la Pénicilline dosage obtenues par des expériences différentes variaient considérablement. Ces variations n'étaient sans doute causées ni par les variations du pH du suc gastrique, ni par les différences d'âge des enfants nés avant terme; mais il semble qu'un facteur plus important soit, dans chaque cas, la réaction individuelle à la Pénicilline, la réaction de

chaque individu variant d'une manière à peu près identique au cours d'expériences différentes.

Sur la base des résultats obtenus, l'auteur a tiré un certain nombre de conclusions touchant la thérapeutique par la Penicilline.

Zusammenfassung

Der Zweck der Untersuchung war, die Möglichkeiten zu erforschen, unter denen Penicillin Frühgeburten oral verabreicht werden kann. Das Material umfasst 18 Fälle, in denen der Penicillin-Titer 48 mal bestimmt wurde. Es wurde gefunden, dass gerade kleine Dosen (4 000—10 000 Einheiten) imstande sind, den Penicillin-Titer des Blutes zu einem genügend hohen therapeutischen Niveau zu steigern (0.06 oder darüber). Die Probe, eine Stunde oder zwei Stunden nach Verabreichung entnommen, zeigte einen genügenden Titer in fast allen Fällen und sogar nach drei Stunden in Dreiviertel der Fälle. Es schien, dass die Verabreichung vor den Mahlzeiten zu etwas höheren Werten führte (aber diese Werte erhielten sich nur für kürzere Zeiträume), als wenn die Verabreichung nach den Mahlzeiten erfolgte. Die Werte des Penicillin-Titers die bei verschiedenen Versuchen erhalten wurden, variierten beträchtlich. Diese Unterschiede beruhten scheinbar nicht auf Unterschieden im pH des Magensaftes noch auf der Verschiedenheit des Alters der Frühgeburten. Jedoch schien ein wichtigerer Faktor zu sein die individuelle Reaktion auf Penicillin, da die Reaktion des Individuums jedesmal in beinahe derselben Weise bei den verschiedenen Versuchen sich änderte.

Auf Grund der gefundenen Resultate hat der Verfasser eine Reihe von Schlüssen gezogen betreffs einer praktischen, planmässigen Penicillin-Therapie.

Sumario

El objeto de la investigación ha sido el estudio de las posibilidades de dar penicilina vía bucal a niños prematuros. El material abarca 18 casos en los cuales el título de penicilina se determinó 48 veces. Se encontró que también pequeñas dosis (4 000—10 000 unidades) pueden aumentar el título de penicilina

de la sangre a un nivel suficientemente alto de la terapéutica (0.06 ó más). Las pruebas sacadas una o dos horas después de haber suministrado la penicilina descubrieron un título suficiente en casi todos los casos y hasta tres horas después en tres cuartas partes de los casos. Se vió que el suministrar la penicilina antes de las comidas conducía a valores un poco más altos, pero estos valores se mantuvieron durante períodos más cortos que los obtenidos al suministrar la penicilina después de las comidas. Los valores de los títulos de penicilina que se obtuvieron en varios experimentos variaban bastante. No parecía que estas variaciones fueran debidas a variaciones de pH del jugo gástrico ni tampoco a variaciones de la edad de los niños prematuros, pero se vió que era un factor de mayor importancia la reacción individual contra la penicilina en cada caso, en vista de que la reacción de cada individuo varía aproximadamente de la misma manera en los diferentes experimentos.

A base de los resultados obtenidos, el autor ha hecho una serie de conclusiones respecto al programa práctico de la terapía de la penicilina.

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FROM THE CHILDREN'S HOSPITAL, MARTINSVEJ, COPENHAGEN.
CHIEF: ARNE ROTHE-MEYER, M.D.

Serum Protein and Blood Urea in Prematures on High Protein Nutrition

by

ARNE ROTHE-MEYER

Two recent contributions have emphasized the benefit of high protein feeding in prematures. LEVINE and GORDON concluded in their work on acidified cow's milk mixtures that were reduced in fat and high in protein that this diet should be preferred to human milk. — By supplementing human milk with an amino acid glycose mixture MAGNUSSON obtained a remarkably increased weight gain in prematures during their first month of life. The conclusions of these authors and of later confirming reports are based principally on the sole criterion of weight gain. Further investigations into the pros and contras of this kind of feeding are needed before the thesis of the preferability of high protein nutrition for prematures can be generalized.

DARROW found a tendency towards acidosis in prematures fed on high protein diet, and similar result were obtained by DUPONT in our series of prematures. This paper deals with investigations into serum proteins and blood urea.

Weight Gain

Dietary experiments along the lines of LEVINE and GORDON and of MAGNUSSON have been carried on for the last three years. Four different types of diet have been used in our series of prematures:

1) *human milk* (H.M.), represented by milk either from the mother or from a human milk bank;

2) *allaitement mixte* in the form of human milk supplemented with $^1/_2$ skimmed citric acid milk (All. Mixte);

3) *artificial feeding* with $^1/_2$ skimmed citric acid milk (Cit. M.);

4) *human milk* with a supplement of *amino acids.*

The half skimmed citric acid milk used in artificial feeding and as a supplement to breast feeding was given in the beginning in diluted form, starting with 60 % dilution, four days later increasing to 70 %, and again four days later ending with undiluted $^1/_2$ skimmed citric acid milk with 5 % sugar. This formula is practically isocaloric with human milk. The feeding quantities could therefore be adapted to the individual requirements of the prematures, thus avoiding pre-formed feeding schemes.

For a similar reason, i.e. avoidance of the necessity of making corrections for fluid intake — the amino acid supplement was given as a powder and without glycose. A total intake of 5 g of protein per kg per day was aimed at, the necessary amount of amino acid being measured in the morning and distributed equally over the various meals of the day. The administration of amino acid supplement was started on the eighth to tenth day of life.

Two different kinds of protein digests have been tried. In a first series, reported to the International Conference of Physicians, London, 1947, the Danish product, *Aminolin Orthana,* an acid hydrolysate, did not show any weight-increasing effect at all. In a new series with another Danish preparation, the enzymatic hydrolysate »*Aminocid Wander*», a weight-increasing effect could be demonstrated. This new series has been included in *Table 1* but it is too limited to permit any conclusions and has therefore been omitted from the following biochemical studies.

The majority of the premature babies included in this work have been transferred to our department from the adjoining municipal *maternity hospital, Martinsvej.* In the beginning of our study the prematures were usually admitted on the ninth—tenth day of life, when the mother was about to be discharged from the maternity home. Therefore we, unlike MAGNUSSON, could

not use the first month of life for investigation and instead chose the period between the fourteenth and forty second days of life. This observation period has been maintained in spite of a new arrangement between the two hospitals for the last two years under which the prematures are admitted to the paediatric hospital direct from the delivery room of the maternity hospital.

Table 1

Mean and variance of the daily weight gain in prematures fed on the different diets.

Diet	Number of Cases	Mean g	Variance	Deviation from Mean of H.M.
	Birth Weight < 2 000 g			
Amino Acid	5	24.6	46.30	−0.2
Human Milk	23	24.8	15.79	—
Allait. Mixte	6	25.8	9.77	1.0
1/2 Sk. Cit. Acid Milk	9	30.0	9.00	5.2[3]
	Birth Weight ≧ 2 000 g			
Amino Acid	4	35.0	33.33	7.2[2]
Human Milk	18	27.8	11.91	—
Allait. Mixte	12	30.9	14.08	3.1[1]
1/2 Sk. Cit. Acid Milk	20	34.0	16.16	6.2[3]
Total	97	—	15.93	

[1] Signifies a probability between 1 % and 5 %.
[2] » » » » 0.1 % » 1 %.
[3] » » » below 0.1 %.

In *Table 1* are recorded the prematures the nutritional studies of whom did not have to be interrupted because of untimely death, discharge, change of formula, or severe complications. Each of the four types of diet has been divided into two subgroups according to whether the birth weight was above or below 2 000 g.

For both these weight groups the *mean values of the daily weight gain* during the period from the fourteenth to the forty second day are significantly higher in the prematures on Cit. M.

than in those on H.M. (i.e., 30 g as against 24.8 g in the low weight group and 34 g as against 27.8 g in the high weight group).

A more detailed analysis of Table 1 may be summarized in the following way:

Birth weight $< 2\,000$ *g*. The mean of Cit. M. diet is significantly greater than the means of H.M., All. Mixte, and amino acid diets. The mean of amino acid diet almost equals the mean of H.M. diet. The mean of All. Mixte is not significantly greater than the mean of H.M. diet.

Birth weight $\geqq 2\,000$ *g*. The means of amino acid, All. Mixte, and Cit. M. are greater than the mean of H.M. diet. The mean of Cit. M. diet is also significantly greater than the mean of All. Mixte.

It is well to remember that the prematures on All. Mixte necessarily represent the least uniform of the dietary groups, including babies fed predominantly on their own mother's milk and those fed mostly on Cit. M.

Serum Proteins and Blood Urea

Blood drawn from the sagittal sinus or a cranial vein was used for the biochemical determinations. Because of inadequate laboratory facilities in the children's hospital, the analyses had to be performed at the »*Medicinsk Laboratorium*» *of Drs.* BIERRING and NIELSEN.

The *serum proteins* were determined by the method of HENRIQUES and CLAUSEN comprising Kjeldahl and using half-saturation with ammonium sulfate for the precipitation of globulin.

Blood-urea was estimated by the urease method of VAN SLYKE and CULLEN.

The determinations of protein and urea were made as far as possible on the seventh—fourteenth—twenty eighth and forty second days of life. Owing to the irregularities of age at admission and nutritional changes, this scheme could not be strictly adhered to, which explains the periods of 0—10, 11—21, 22—35 and 36—65 days used in Table 2 and the statistical report. Neither the proteins nor the blood urea showed any correlation with the birth weight, which has therefore been disregarded. As has been mentioned before, the dietary group on amino acid supplement was omitted from the biochemical studies.

Table 2

Mean and variance of serum protein and blood urea in prematures fed on the different diets.

Age in days	Diet	Protein (Means)				Blood Urea (Means)		
		Number of Cases	Total P g%	Albumin g%	Globulin g%	Number of Cases	Logar. Mean	mg%
0—10	Human Milk	13	4.77	3.26	1.51	17	1.23	17.0
	Allaitement Mixte	7	5.24	3.87	1.37	11	1.37	23.4
	1/2 Sk. Citric Acid Milk	16	5.29	3.66	1.63	21	1.49	30.9
11—21	Human Milk	29	4.87	3.52	1.35	34	1.05	11.2
	Allaitement Mixte	12	5.41	3.73	1.68	12	1.31	20.4
	1/2 Sk. Citric Acid Milk	17	4.83	3.78	1.05	20	1.41	25.7
22—35	Human Milk	30	4.40	3.27	1.13	30	0.96	9.1
	Allaitement Mixte	10	4.79	3.68	1.11	11	1.37	23.4
	1/2 Sk. Citric Acid Milk	21	4.76	3.49	1.27	22	1.43	26.9
36—65	Human Milk	10	4.17	3.22	0.95	11	0.95	8.9
	Allaitement Mixte	6	4.62	3.42	1.20	8	1.39	24.6
	1/2 Sk. Citric Acid Milk	16	4.60	3.46	1.14	18	1.51	32.4
	Total	187	—	—	—	215	—	—
	Variance	—	0.203	0.239	0.222	—	0.0261	—
	Degrees of Freedom	—	175	175	175	—	203	—

Serum Protein

Two interesting findings appear in Table 2 (and Fig. 1).

1) During the period from the seventh to the fiftieth day of life, the level of *total protein* decreases with increasing age in all three dietary groups investigated. While the *albumin* level did not undergo any significant changes, the *globulin* level showed a decrease similar to that of the total protein. On account of irregularities of the curves certain reservations have to be made for the globulins.

2) During this same age period the *level of total protein* in prematures fed on H.M. diet is significantly lower than the level in prematures fed on Cit. M. and All. Mixte. A single exception to this finding — during the age period eleven—twenty one days — may be safely disregarded.

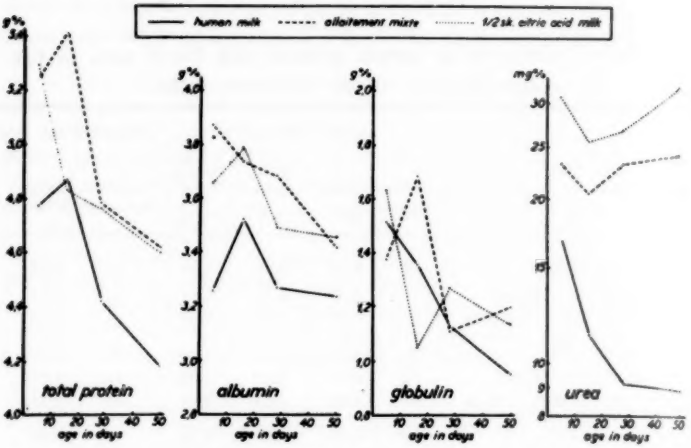

Fig. 1. Means of total protein, albumin, globulin, and blood urea in prematures from seventh to fiftieth day of life.

The *albumin level* follows that of total protein, showing constantly lower levels in prematures on H.M. diet than in prematures on the two other kinds of diet.

As to *globulin*, no such significant differences between H.M. diet and the other two diets were found.

In conclusion it may be stated that the level of serum protein is lower in prematures on H.M. diet than in prematures on Cit. M. and on All. Mixte, the difference being due to albumin, while the globulin does not undergo any of these changes. A comparison of Cit. M. and All. Mixte did not show any significant differences with regard to the protein levels.

Blood Urea

These investigations also revealed two interesting facts (Table 2 and Fig. 1).

1) The *urea levels* of prematures on H.M. diet decrease significantly during the age period from the seventh to the fiftieth day of life. In babies on Cit. M. and on All. Mixte such a decrease does not occur.

2) During this same age period the urea levels in prematures on Cit. M. and on All. Mixte are significantly higher than those of prematures on H.M. (Cit. M. again is significantly higher than All. Mixte).

Conclusions

These investigations have shown that during the first fifty days of life the *level of serum protein* in prematures on high protein nutrition is significantly higher than in prematures fed on human milk. While it is better to refrain from any biological conclusions, it may safely be stated that these findings may throw some interesting light on the question of the influence of nutritional factors upon the serum protein.

The *level of blood urea* in prematures on high protein diet is significantly higher than in prematures fed on human milk. As on first sight one may well be tempted to interpret these findings as an increased strain upon the organism, it is well to remember that — as far as we know — these values are high values within the normal range, thus representing a biological problem the interpretation of which still is missing.

Finally, these findings tend to emphasize the fact that any biochemical studies in prematures — and especially the establishment of the so-called normal values — may be jeopardized by lack of due regard to the feeding of the individuals investigated.

Extract from Statistical Report

The statistical analysis and extract have been made by ARNE NIELSEN, Lic. Act., statistician to the Danish Cancer Register.

Weight Gain

The daily weight gain during the period from the fourteenth to the forty second day of life was dependent on the birth weight of the infant. As the distribution of the infants according to birth weight was not identical in the four nutritional groups (e.g. prematures on H.M. diet had a lower birth weight than prematures on Cit. M. diet, see Table 1), a division into two weight groups, one with birth weight of less than 2 000 g and one with birth weight exceeding 2 000 g, was made. The four different kinds of nutrition were compared for each of these weight groups.

An estimate of the mean and the variance (see Table 1) was made for each of the resulting eight groups, the distribution of the infants according to daily weight gain in each of the groups being approximately normal. By a »false χ^2 test» it could be proved that the estimates of the variances did not differ so much that a homogeneous variance for all eight groups was unacceptable. The estimate of this variance was 15.93 with 89 degrees of freedom. The estimate of the standard variation was therefore 3.99 g.

The final comparison of the means of the four kinds of nutrition could now be performed by a t-test. The last column of Table 1 expresses the difference (in g) between the means of the three diets amino acid, allaitement mixte, and $^1/_2$ skimmed citric milk and the mean of the H.M. diet. The asterisks indicate the probability of the deviation. A probability of less than 5 % refutes the hypothesis that prematures on the two diets compared show an equal daily weight gain.

Total Protein, Albumin, and Globulin

No correlation between birth weight and total protein, albumin, and globulin could be established. As all three proteins decreased with increasing age (see Fig. 1), a division of the material into four age groups, 0—10 days, 11—21 days, 22—35 days, and 36—65 days, was made. In each of these age groups there was only one observation on each individual, but frequently there were observations on the same infant in several age groups.

As the distribution according to total protein, albumin, and globulin was approximately normal, an estimate of the mean and the variance (see Table 2) could be made for each group. By a »false χ^2 test» it could be proved that for each of the three criteria there was a uniform variance for all groups. The estimates of these have been recorded in Table 2.

By a t-test the comparison of the means of the three kinds or nutrition could now be performed, infants on amino acid having been excluded.

Total Protein. Prematures on H.M. diet had significantly lower levels of total protein than prematures on both All. Mixte and Cit. M. In the age group 11—21 days, however, the mean of Cit. M. was less — but not significantly less — than the mean of H.M. prematures. There were no significant differences between the means of All. Mixte and Cit. M. infants with the exception of the age period 11—21 days, when the previously mentioned low mean of the Cit. M. group was significantly less than the mean of All. Mixte.

Albumin. The All. Mixte and Cit. M. groups both had a significantly higher mean than the H.M. group, the two first mentioned groups showing almost uniform variations.

Globulin. All three nutritional groups showed equal levels with the exception of the low value of the Cit. M. group in the age period 11—21 days, which showed a significant difference from the mean of the All. Mixte group.

Blood Urea

The statistical analysis was made along the same lines as for the proteins. No correlation between birth weight and blood urea could be established.

While the urea values for H.M. prematures decreased with increasing age, the urea values of the infants on All. Mixte and on Cit. M. remained at a constant level (Fig. 1).

As the logarithmic urea values showed an approximately normal distribution, the estimates of the means and of the variance were based on logarithms. Here also a general estimate of the variance of all groups as a whole was possible (Table 2).

In all age groups — including the age 0—10 days — the mean of the H.M. group was significantly less than the mean of the groups on All. Mixte and on Cit. M. The separate age periods did not show any significant difference between the All. Mixte and Cit. M. groups' but as a whole the Cit. M. values were significantly higher than the All. Mixte values.

Summary

The beneficial effect of high protein nutrition as claimed by LEVINE and GORDON with acidified cow's milk mixtures reduced in fat and by MAGNUSSON with an amino acid supplement to human milk has been confirmed as regards the criterion of weight gain.

During the period from the seventh to the fiftieth day of life the *level of total protein decreases* with increasing age in prematures fed on human milk (H.M.), on allaitement mixte (All. Mixte), and on $^1/_2$ skimmed citric acid milk (Cit. M.). This decrease is caused by *globulin*, the albumin fraction undergoing no significant changes.

During this same age period the level of *total protein is lower* in prematures fed on human milk than in prematures on Cit. M. and All. Mixte, the difference being due to *albumin*.

The level of *blood urea* in prematures fed on *human milk decreases* during this same age period, while such a decrease does

not take place in prematures fed on Cit. M. and on All. Mixte. The *urea levels* of the two last mentioned dietary groups are significantly higher than the levels of the human milk group.

Résumé

L'effet bienfaisant de la nutrition en protéines élevées — que LEVINE et GORDON ont préconisé par des mélanges de lait de vache acidifié et écrèmé, et MAGNUSSON par une addition d'amino-acide au lait humain — a été confirmé par le critérium de l'augmentation des poids.

Du 7ème au 50ème jour de la vie, le *niveau de protéine totale* diminue avec l'âge chez les enfants nés avant terme nourris de lait human (H.M.) chez ceux nourris par allaitement mixte (All. Mixte), et chez ceux nourris de lait écrèmé et acidifié (Cit. M.). Cette diminution est causée par la *globuline;* la fraction d'albumine n'est pas modifiée d'une manière significative.

Pendant cette période de la vie, le niveau de *protéine totale* est plus bas chez les sujets nés avant terme nourris de lait humain que de Cit. M. et par allaitement mixte, la différence étant causée par l'albumine.

Le niveau *d'urée sanguine,* chez les sujets nés avant terme *nourris de lait humain diminue* pendant cette même période de l'existence, alors que cette diminution n'existe pas chez les sujets nourris avant terme nourris de Cit. M. et par All. Mixte.

Les niveaux d'urée des deux derniers groupes diététiques sont, d'une manière très significative, plus élévés que les niveaux des groupes nourris de lait humain.

Zusammenfassung

Die günstige Wirkung von hochwertiger Proteinernährung — nach dem Vorschlag von LEVINE und GORDON mit gesäuerten Kuhmilchmischungen, die in Fett reduziert ist und nach MAGNUSSON mit einem Aminosäurezusatz zur Frauenmilch — ist hinsichtlich der Gewichtszunahme als Masstab bestätigt worden.

Während der Zeit vom 7. bis 50. Lebenstage sinkt *das Niveau des Gesamt-Proteins* mit zunehmendem Alter bei Frühgeburten, die mit Frauenmilch ernährt wurden, bei Allaitement mixte und

bei Ernährung mit $^1/_2$ entrahmter zitronensaurer Milch. Diese Verminderung ist durch *Globulin* verursacht, während das Albumin keinen bedeutenden Veränderungen unterliegt.

In derselben Altersperiode ist das *Niveau des Gesamt-Proteins* bei Frühgeburten mit Frauenmilchnahrung niedriger als bei Frühgeburten mit Zitronenmilchernährung oder bei Allaitement mixte. Der Unterschied hängt von dem *Albumin* ab.

Das Niveau des Blutharnstoffs bei Frühgeburten mit *Frauenmilchnahrung* sinkt während ebendieser Altersperiode, während eine solche Abnahme nicht stattfindet bei Frühgeburten mit Zitronenmilchernährung und mit Allaitement mixte. *Das Harnstoffniveau* der beiden zuletzt erwähnten Diätgruppen ist deutlich höher als das Niveau der Frauenmilchgruppe.

Sumario

El efecto beneficioso de nutrición con alto contenido de proteína ha sido confirmado por lo que se refiere al criterio de aumento de peso — lo cual ya había sido indicado por Levine y Gordon, mediante mezclas de leche de vaca con reducido contenido da grasa y por Magnusson mediante unsuplemento de aminoácido a leche humana.

Durante el período comprendido entre el séptimo y el cincuenteno día de vida el *nivel de proteína total disminuye* en grado creciente en prematuros alimentados con leche humana (H.M.), con alactación mixta (All. Mixte) y con leche semi-desnatada de ácido cítrico (Cit. M.). *La globulina* produce esta disminución y la fracción de albumen no sufre ningún cambio de importancia.

Durante este mismo período de edad *el nivel de preteína total es más* bajo en prematuros alimentados con leche humana que en prematuros alimentados con Cit. M. y All. Mixte. La diferencia es debida al albumen.

El nivel de *urea de sangre* en prematuros alimentados *con leche humana* disminuye en este mismo período de edad, mientras que una disminución de esta clase no tiene ligar en prematuros alimentados con Cit. M. y con All. Mixte. *Los niveles de urea* de estos dos grupos dietéticos recién mencionados son notablemente más altos que los niveles del grupo alimentado con leche humana.

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Diaplacental Infection of the Foetus With the Virus of German Measles Despite Immunity of the Mother

Analogous Observations in Smallpox

by

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GREGG and SWAN were the first to report characteristic malformations in children born of mothers who had german measles in early pregnancy. These malformations consisted of a combination of cataract, blindness, congenital heart lesions, deafness, mental retardation, etc. The report of GREGG and SWAN was soon followed by conforming publications by other authors. It has been recommended that: 1. females be exposed to german measles during childhood so that they become immune; 2. pregnant women who have never had german measles avoid exposure to that disease, particularly during the first four—five months of their pregnancy; 3. pregnancy be terminated if women come down with german measles within the first three—four months of pregnancy.

These recommendations are plausible but they do not cover the whole problem. GREGG and SWAN found that similar congenital combined defects occur in children even when no history of german measles can be established during their mothers' pregnancy. It may be, of course, that infections caused by another virus may have the same effect.

WARKANY made outstanding contributions to the problem of malformations in animals due to nutritional (vitamin) deficiencies. He also studied other causes of malformations in human beings and animals and published his results in the second volume of the »Advances in Pediatrics». On page 46 he described a child with the above mentioned malformations born of a mother who was unaware of any illness during pregnancy, but two of her

older children had had german measles when she was in the second month of this pregnancy and she took care of them (observation by Dr. B. Berliner).

Accordingly an important problem arises: whether a mother immune to german measles, either without a previous manifestation of the disease or because she had german measles during childhood, can expose herself to german measles without endangering the foetus.

For several years I have been concerned about such a possibility, as analogous observations have been made in smallpox. Studying the history of smallpox and smallpox-vaccination, I found reports that pregnant women should never take care of smallpox patients even if they had been successfully vaccinated or had had a fully developed smallpox disease. The foetus may escape the infection, but the danger exists that it may become infected and die, be born with recent smallpox, or be born with scars proving that it became infected and went through smallpox during intrauterine life.

Thus the immunity of the mother due to successful vaccination with cowpox vaccine or due to having had the disease as a rule protects her but does not always protect the foetus inside the uterus.

These observations may be explained by the following theory. The immunity of the mother to smallpox is either humoral or cellular. The humoral immunity is based upon the presence of antibodies in the circulating serum. These antibodies kill the invading virus instantly (Immediate Reaction), and mother and child remain free from smallpox. In cellular immunity, circulating free antibodies have already disappeared but can be rapidly reproduced. This cellular immunity cannot prevent the circulation and multiplication of the virus in the mother until the antibodies are mobilized. This specific allergy guarantees immunity of the mother. The antibodies entering the circulation will destroy the virus rapidly enough to protect the mother, as the virus had only a short time for multiplication. But in the short time between invasion and the mobilization of antibodies, the living virus circulates in the blood of the mother, reaches the

uterus, and infects diaplacentally the non-immune foetus, bringing about the disease. Whether or not there must be a defect in the placenta facilitating the passage of the virus is a separate problem (CHAUTREIL, FUMÉE, and KALTENBACH).

In the following survey I list the literature concerning observations in smallpox. There are reports on about forty children. It is likely that many more cases have been observed but not published.

If these occurrences are possible in smallpox, we must concede the possibility of analogous observations in other diseases, including german measles.

Cases and Remarks Illustrating the History of Pregnancy Complicated With Smallpox

BARNES: In Philosophical Transactions, Vol. 46, this case is reported. A woman great with child, having herself had variola long ago, nursed a maid servant with the disease. At the proper time she brought forth a healthy female child in whose skin Dr. Watson discovered evident marks of variola. Dr. Watson pronounced that the child would be free from future infection.

After four years her brother was inoculated at the same time as herself with pus from the same patient. The boy had the regular eruption. The girl did not inflame or suppurate. On the tenth day she suddenly turned pale, languished for two days, and then was well.

Dr. JENNER relates a case told him by Mr. Henry Gervis, a surgeon at Ashburton. Mr. Gervis vaccinated a pregnant woman in her last month, variola prevailing in the village. Her eight children had been inoculated with variolous matter the day before. She went through the vaccine disease and was delivered of a female child presenting an eruption resembling variola in an early stage. This was five weeks after her exposure to the variolous infection of her own children. Mr. Gervin inoculated successfully with pus taken from the infant's pustules.

JOHN HUNTER relates a similar case.

CHAMP quotes the following reports:

MEJEAN (Montpellier) observed two cases of congenital variola. In the first case the mother never in her life showed any symptoms of variola or any eruption suggesting variola. She delivered a baby showing a small number of whitish and slightly elevated papules. In the village there was an epidemic of variola.

DEVILLIERS (1842) describes a baby born prematurely in the seventh

month of pregnancy. The body of the baby showed variola pustules, although the mother showed no trace of the disease.

DEPAUL (1851) saw a foetus of a mother six and a half months pregnant covered with smallpox pustules. In 1880 he published another case of congenital smallpox, both cases without infection of the mother.

GUBLER published a new observation of this kind after a publication of CHAUTREUIL. The latter observed a woman six months pregnant and always healthy who delivered two foetus, one of them showing an eruption of variola, whereas the other twin had no symptoms. The mother had never had any symptoms of variola.

BLOT reported at the same meeting of the academy observation of a woman who had always been healthy and was successfully vaccinated in infancy. She aborted in the fifth month of pregnancy. The foetus showed over eighty pustules without predilection. This eruption was found not only in the skin but also in the digestive tract.

NOBLES de Rennes: A woman six months pregnant took care of one of her daughters with variola. Ten days later she delivered a child covered with variola pustules. There were no symptoms in the mother.

CHAIGNEAU confirmed this observation and reported three more. The first, a woman working as »fille de salle» in a smallpox ward, gave birth half way through the seventh month of pregnancy to a foetus showing traces of smallpox pustules. The mother had never contracted variola before. The second observation is similar. The mother had never had any symptoms of variola. She delivered a baby with umbilicated small pustules. The third child observed was born with an eruption of non-umbilicated small pustules. The mother had had symptoms of smallpox neither before nor during her pregnancy. PLASTARD, DEPAUL, EBEL, BOUCHUT, JENNER, and VON SPEREN reported similar cases. CHAMPS thinks that perhaps the mother had only a few pustules which were overlooked or that the immunity of the mother was sufficient for her but not for the foetus.

In his article »Smallpox» in Ziemssen's Handbook, CURSCHMAN writes as follows on page 328. During a severe epidemic of smallpox a midwife forty years old became ill with rigor followed by violent fever, headache, and pain in the back — apparently the initial stage of smallpox. On the fourth day, however, she was free from fever and in spite of the most careful examination exhibited no trace of the expected eruption. Ten days after the onset of these symptoms — when she was feeling perfectly well — she gave birth to a child covered with a smallpox eruption, evidently just appearing, which developed still further. The child died during the stage of suppuration.

LELIÈVRE quotes an observation made by LEGROS of a woman who in the fifth month of pregnancy aborted a foetus covered with variola pustules. The mother had been successfully vaccinated. She thought

that the infection was due to intercourse five months previously with a man convalescing from variola. This cannot be correct. The mother may have exposed herself to variola without her knowledge.

MICHEL COUREMENOS quotes in his Thèse de Paris, 1901, many authors with similar observations, some of them taken from publications mentioned above. Others could not be found because the Academy of Medicine in New York does not have a complete collection of the Thèses de Paris.

Conclusions

A pregnant woman should under no circumstances take care of patients suffering with german measles nor come in contact with such patients even if she has previously had german measles. It may be that the danger of infecting the foetus is less great when the mother has had german measles only one or two years before pregnancy, rather than many years before, because circulating antibodies from a not-distant active disease may still be present, but practically the danger still exists that there is only cellular immunity. We may go even further and teach that pregnant women should not come in contact with any infectious diseases (particularly virus diseases).

Further studies are necessary to show which diseases are particularly dangerous to the foetus. It is possible that infants born with symptoms of cerebral disease or cerebral damage are victims of intrauterine infections of a mother herself immune to such an infection.

Summary

The problem of the transmission of german measles to the foetus of a mother immune to the disease is discussed. The occurrence of transmission is already established (WARKANY). Analogous observations in smallpox have been published. The literature of the latter is reviewed. The consequence of such transmissions in different virus diseases constitutes a warning that a pregnant mother, even if she has had german measles in childhood or is herself immune to german measles without any previous history thereof, should not take care of her children or other patients suffering from german measles. The virus may

invade the circulation of the mother and reach the foetus in spite of the immunity of the mother. The difference between cellular and humoral immunity of the mother is given as explanation of the infection of the foetus. Probably only humoral immunity of the mother would prevent the infection of the foetus. Cellular immunity would protect only the mother, not always the foetus. Even rapid (accelerated) reproduction of antibodies may come too late to prevent the passage of the virus through the placenta to the foetus.

Résumé

Infection diaplacentaire du fœtus par le virus de la rubéole malgré l'immunisation de la mère. Observations analogues pour la variole

Le problème de la transmission de la rubéole au fœtus de mères immunisées contre la maladie est discuté. La possibilité de la transmission est déjà établie (WARKANY). Des observations analogues sont publiées concernant la variole. Il est fait un compte rendu des écrits traitant de cette dernière. La conséquence de telles transmissions dans différentes maladies à virus est un avertissement qu'une mère enceinte, même si elle a eu la rubéole dans son enfance ou si elle est immunisée contre cette maladie sans histoire antérieure de rubéole, ne devrait pas soigner ses enfants ou quelque autre malade souffrant de rubéole. Le virus peut envahir la circulation de la mère et peut atteindre le fœtus malgré l'immunité de la mère. La différence entre l'immunité cellulaire et humorale de la mère est donnée comme explication de la contamination du fœtus. Seule l'immunité humorale de la mère empêche d'une manière presque totale la contamination du fœtus. L'immunité cellulaire de la mère ne protégerait que cette dernière de façon suffisante, et pas toujours le fœtus. Même une production rapide des anticorps peut arriver trop tard pour empêcher le passage du virus à travers le placenta, jusqu'au fœtus.

Zusammenfassung

Diaplazentare Infektion des Fötus mit dem Rötelnvirus trotz der Immunität der Mutter. Analoge Beobachtungen bei Pocken

Das Problem der Übertragung von Röteln auf den Fötus bei Müttern, die gegen diese Krankheit immun sind, wird diskutiert. Die Tatsache der Übertragung ist bereits festgestellt (WARKANY). Analoge Beobachtungen werden bei Pocken gemeldet. Die Literatur über diese Fälle wird besprochen. Die Folge solcher Übertragungen bei verschiedenen Viruserkrankungen ist eine Warnung für die schwangere Mutter, nicht die Pflegung ihrer Kinder oder anderer Patienten, die an Röteln erkrankt sind, zu übernehmen, selbst wenn sie Röteln in ihrer Kindheit gehabt hat oder ohne vorherige Erkrankung immun ist. Der Virus kann in den Blutkreislauf der Mutter eindringen und kann, trotz der Immunität der Mutter, den Fötus erreichen. Der Unterschied zwischen der zellularen und humoralen Immunität der Mutter wird als Erklärung für die Infektion des Fötus angeführt. Nur die humorale Immunität der Mutter würde wahrscheinlich die Infektion des Fötus verhindern können. Die zellulare Immunität der Mutter würde nur die Mutter genügend vor der Krankheit schützen, aber nicht immer den Fötus. Selbst die beschleunigte Neubildung von Antikörpern kann zu spät kommen, um die Passage des Virus zum Plazenta verhindern zu können.

Sumario

Infección transplacentaria del feto con el virus del Sarampión germano no obstante la presencia de inmunidad en la madre. Análogas observaciones en la viruela

Se discute el problema de la transmisión del sarampión germano a los fetos, de madres inmunes a esta enfermedad. La constatación de esta posible transmisión fue ya establecido por (WARKANY). Observaciones analogas han sido publicadas en el caso de la viruela. Se pasa revista a la litteratura respecto a esta ultima enfermedad. La consecuencia, de la posibilidad de transmisión de estos distintos virus, es la advertencia de que una madre embarazada, habiendo tenido el sarampión durante su infancia, o siendo inmune al sarampión germano sin historia clinica previa

de enfermedad, no se preócupara de sus hijos u otras personas que tengan sarampión. El virus puede asi invadir la circulación de la madre y puede alcanzar al feto a pesar de la inmunidad de la madre. Se da como explicación de la infección del feto, una diferencia en la madre entre inmunidad celular y humoral. Probablemente solamente una inmunidad humoral en la madre pueda prevenir la infección del feto. La inmunidad celular en la madre solamente protegeria suficientemente a la madre contra la enfermedad, pero no siempre al feto. Mismo una reproducción acelerada de anticuerpos puede resultar tardía para prevenir el pasaje del virus a travez de la placenta del feto.

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Mortality Among Premature Infants

by

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Mortality among premature babies is a popular subject in medical literature. It is usually stated to be about 25—30 %, though there is striking divergence among figures from different clinics. If we choose only from among the figures published in the past few years, we find on the one hand such low ones as 8.1 % (FIELD 1943), 9.5 % (BARNES and WILLSON 1942), and 13.4 % (CROSSE 1949), and on the other such a high one as 59.1 % (HALLMAN and SOMERSALO 1947). One finds it difficult to believe that the methods of treatment among paediatricians are so divergent that they can be the cause of such differences. Instead, one is inclined to believe that a bias in the form of selection has made itself felt and that the sample data are not always comparable.

Some factors will be mentioned below that ought to be taken into account more generally in studies bearing on the prognosis of premature infants. In addition, the author will submit the results of a study of this kind of a series of cases from a Swedish provincial hospital. In these cases the elements of selection have been eliminated to the greatest possible extent.

In a study of the prognosis of premature children, the meaning of the term must first be made clear. In 1919 YLPPÖ defined premature infants as those that »come into the world with a birth weight of less than 2 500 g». The American Academy of Pediatrics made the following statement in 1935: »A premature infant is one who weighs 2 500 g or less at birth», a definition which was recommended by the International Committee at Geneva in 1937. *A priori* it may be suspected that the mortality difference

in cases collected on the basis of YLPPÖ's definition or that of the American Academy of Pediatrics will not be great — though the mortality in the former material would naturally be higher. Nevertheless we are obliged to keep the two concepts distinct. YLPPÖ's classification still appears to be the one employed most in European literature, but there seems to be a tendency to go over to the American view.

A division into weight-classes of the same size is also a necessary condition before a comparison may be made between the data of different authors. A suitable division of this kind is that employed by HESS.

It is known that the mortality among newborn infants is greatest on the first day of life, being highest in the smallest babies. To obtain a correct view of the mortality among premature babies in hospital practice we ought therefore to exclude from analysis those who have been admitted to the paediatric department *later* than the first day of life. These infants obviously represent a selection, since they have survived the first critical day and are therefore more viable than those who have succumbed. On the other hand, the prognosis for these later admissions may also be bad, *e.g.* if their care has been unsatisfactory.

It is a matter of course that the mortality in a given series of patients is dependent upon the length of the observation period. As a rule workers dealing with statistics concerning prematurity do not class children as dead if they have been discharged living from the hospital. Since the period of medical supervision is dependent on social, technical, and other factors, this means the introduction into the statistics of factors that vary for different hospitals and countries. To secure a correct view of the prognosis it is accordingly necessary for the length of the observation time to be stated.

In a series made up of premature infants born and cared for in a maternity hospital the elements of selection assert themselves less forcefully. Yet the fact remains that complicated pregnancies have a tendency to accumulate at women's clinics, especially at those where there is a shortage of accommodation. It is a known fact that diseases and other complications among pregnant women

increase not only the frequency of prematurity but also the premature mortality. This factor undoubtedly also has an effect on the different data. It would seem practically impossible, however, to avoid this element of selection, though the situation can be judged to some extent if data are available concerning the prematurity rate in the obstetric material.

These factors influence in the first place the total mortality figures in a series of premature cases. But a comparison between the same weight-classes of different authors may also be impossible if for example the number of infants admitted for care at a late stage varies in the different series, or if account has not been taken of the period of observation.

To make prematurity statistics from different hospitals comparable, it accordingly seems indispensable to include only such infants as come under treatment on the first day of life, but then to include all of these, malformed babies, idiots, and so on. A series of this kind is submitted below. It was collected from the Obstetric and Paediatric Departments of the Central Hospital of Kristianstad for the period May 1940—Dec. 1947. Babies born alive in the Obstetric Department with a birth weight of 2 500 g or less amounted during this period to 4.9 % of all the children born alive. The figure suggests that no accumulation of complicated obstetric cases had taken place. All babies above 750 g in weight who had shown signs of life were included. The survivors were followed up — or information obtained about them — for at least one year. The number of premature infants who came under treatment from the first day of life was 518 according to YLPPÖ's definition and 548 according to that of the American Academy of Pediatrics. Of these, four discharged living could not be followed up throughout the period mentioned. The rest are recorded in Tables 1 and 2.

The treatments we gave these children were as follows. 1) Continuous administration of oxygen and warmth during the first period; the majority of the smallest babies were cared for in self-regulating incubators. — 2) Vitamin K intramuscularly until the prothrombin index stayed above 60 for some days. — 3) Vitamin C, 50—100 mg intramuscularly daily, the first two or three days. From the second or third week about 50 mg daily by mouth. — 4) Oxedrin (sympathol)

daily during the first week. — 5) No feeding the first twenty four hours. After that, breast milk fed with a tube and slowly increased to about 150 g on the seventh day. Usually six feeds per twenty four hours. — 6) From the first week, addition of casein hydrolysate (Aminosol Glycose Vitrum) in doses of up to 2 ½ g casein hydrolysate per kg and day until a body weight of 2 000 g was reached. — 7) Usually in the third week, addition of citric-acid whole milk, increasing to one part to two parts of mother's milk. — 8) In cases of great decrease in weight, parenteral administration of Ringer's solution. — 9) From third week, vitamins D and A, increasing to about 4 000 and 10 000 I.U. daily. — 10) As a rule the babies were kept in the Paediatric Department until they had attained a body weight of 2 500—3 000 g.

Table 1

Mortality among premature babies (as defined by YLPPÖ). Observation time: one year.

Weight in Grams	Boys		Girls		Boys and Girls	
	Cases	Mortality %	Cases	Mortality %	Cases	Mortality %
750— 999	0	—	2	100	2	100
1 000—1 249	16	68.8	15	86.7	31	77.4
1 250—1 499	16	81.2	19	57.9	35	68.6
1 500—1 999	73	31.5	59	30.5	132	31.0
2 000—2 499	137	9.5	177	8.5	314	8.9
750—2 499	242	24.8	272	21.7	514	23.1

From Tables 1 and 2 it will be seen that the mortality for boys as well as for girls is numerically greater in the series of cases collected on the basis of YLPPÖ's definition than in that based on the definition of the American Academy of Pediatries, though the difference is only 0.9 ± 2.58 %. Hence in a series of this size there is no statistically significant difference. It is also evident from the tables that the mortality is somewhat greater among boys (the difference is 3.3 ± 1.23 %).

In the larger material (Table 2) the mortality is 22.2 ± 1.78. Compared with most of the earlier published collections, this is a low figure. Compared with the above-mentioned American series and the English (CROSSE), the results are not so good.

Table 2

Mortality among premature babies (as defined by the American Academy of Pediatrics). Observation time for material from Kristianstad: one year; in material from Birmingham: four weeks.

Weight in Grams	Kristianstad 1940—1947						Birmingham 1931—1946	
	Boys		Girls		Boys and Girls		Boys and Girls	
	Cases	Mortality %	Cases	Mortality %	Cases	Mortality %	Cases	Mortality %
751—1 000	1	100	2	100	3	100	21	96.6
1 001—1 250	15	66.7	18	83.3	33	75.8	94	62.7
1 251—1 500	17	76.5	19	63.2	36	69.4		
1 501—2 000	77	31.2	62	25.8	139	28.8	238	20.1
2 001—2 500	144	9.0	189	7.9	333	8.4	788	3.8
751—2 500	254	24.0	290	20.7	544	22.2	1 141	13.4

In Table 2 CROSSE's excellently treated and carefully reported material from Birmingham has been included for purposes of comparison. Her material resembles the present writer's except for the fact that her period of observation was only four weeks. If the time of observation in the present material is set at four weeks, the mortality will be 20.0 ± 1.72 %. It will be noticed from Table 2 that CROSSE shows better results in all weight-classes.

Table 3 sets forth the mortality in relation to the child's age. To make the material comparable with CROSSE's the mortality data have been computed on the basis of an observation period of four weeks. It will be seen that the deaths among the premature babies alive at birth in the present author's material were highest in the first week, 17.0 %, while only 3.0 % of the babies died after this time. Comparison between the materials shows that CROSSE's work in Birmingham has had a lowering effect on the mortality in the first week, especially from the second to the seventh day of life. As the care of the premature infants in the Kristianstad series may on the whole be regarded as normal treatment at a Swedish paediatric clinic, it follows that a further decrease in infant mortality in Sweden, especially among premature children,

Table 3

Mortality among live-born premature babies (as defined by the American Academy of Pediatrics) during the first four weeks of life.

Age at Death	Kristianstad 1940—1947		Birmingham 1931—1946	
	% Deaths	% Live Births	% Deaths	% Live Births
Less Than 24 Hours.....	44.0	8.8	50.6	6.8
24—48 Hours.....	14.7	2.9	11.0	1.5
48 Hours to 1 Week	26.6	5.3	19.0	2.5
1—2 Weeks	7.3	1.5	13.6	1.8
2—3 Weeks	6.4	1.3	5.2	0.7
3—4 Weeks	1.0	0.2	0.6	0.1
All Ages	100.0	20.0	100.0	13.4

might be obtained by the adoption of more energetic measures for the care of premature babies during more especially the second to seventh days of life.

Summary

The author suggests some lines along which data concerning premature babies should be arranged and worked up in order to permit comparisons between materials from different centers. Mention is made of CROSSE's data from Birmingham as a model worthy of being followed. A comparison between her series of cases and a series from a Swedish provincial hospital shows that the premature mortality which plays so important a part in infant mortality should admit of being lowered by energetic measures during more especially the second to seventh days of life.

Résumé

La mortalité chez les enfants nés avant terme

En quelques lignes l'auteur suggère de présenter et grouper sous un angle de vue plus large les informations concernant les

enfants nés avant terme de façon à permettre une comparaison entre les rapports provenant de différents centres.

Comme exemple à conseiller il mentionne les résultats de CROSSE, de Birmingham. Une comparaison faite entre ses informations et celles d'un hôpital suédois de province montre qu'on peut admettre que la mortalité des enfants nés avant terme, facteur si important de la mortalité infantile, est susceptible d'être réduite par des mesures énergiques, plus spécialement du 2ème au 7ème jour après la naissance.

Zusammenfassung

Die Sterblichkeit bei Frühgeburten

Der Verfasser schlägt einige Richtlinien vor, um Daten, die sich auf Frühgeburten beziehen, mehr allgemein aufzustellen und auszuarbeiten, und um die Möglichkeit zu bieten, das Material aus verschiedenen Gebieten zu vergleichen. Als nachahmenswertes Vorbild werden die CROSSE'schen Daten aus Birmingham erwähnt. Ein Vergleich zwischen diesem Material und einem aus einem schwedischen provinzialen Krankenhaus zeigt, dass die Sterblichkeit bei Frühgeburten, ein so wichtiger Faktor bei der Kindersterblichkeit, durch energische Massnahmen, die ganz besonders vom zweiten bis siebenten Lebenstag an zu ergreifen sind, herabgesetzt werden könnte.

Sumario

La mortalidad en los niños prematuros

El autor sugiere lineas directrices segun las cuales, todos los datos concernientes a niños prematuros, deben de ser organizados de tal manera y trabajarse en tal forma, que permita realizar una comparación entre el material de los distintos centros.

Como modelo que vale la pena seguirse se mencionan los datos de CROSSE de Birmingham. La comparación de su material con el de un hospital de provincia de Suecia, demuestran que la mortalidad de los prematuros, un factor tan importante en la mortalidad infantil, puede ser disminuido por medio de medidas enérgicas, especialmente en el curso del 2° al 7° dia de vida.

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On the Staub-Traugott Effect in Healthy Children and in Children With Coeliac Disease

by

OLLI SOMERSALO

If two consecutive glucose tolerance tests are performed, it is found that the second causes a lesser rise in the blood sugar level than the first. This was discovered by HAMMAN and HIRSCHMAN in 1919 (1) and by STAUB (2) and TRAUGOTT (3) in 1921—22. This phenomenon, which came to be named after the two last-mentioned authorities, was later investigated with peroral glucose tolerance tests e.g. by GOETZKY (4), who found a Staub effect in a five month old infant; FOSTER (5); and SCHÖNFELD (6), who found an inverted Staub effect in children — i.e. the second blood sugar curve showed a greater rise than the first. A Staub effect is also obtained with intravenous tolerance tests (7, 9, 13). According to HIMSWORTH (7) the »i.v.» Staub effect is clearly manifested if the test person has been on a diet rich in carbohydrates, but with a diet poor in carbohydrates a very clear inverted Staub effect is obtained; the tolerance finally improves and the Staub effect manifests itself only if many tolerance tests (ten or more) are performed in sequence.

After the discovery of insulin the Staub effect was at first explained as meaning that the first sugar dose stimulated the insulin production on the pancreas, with the result that there was a surplus of insulin in the blood during the second tolerance test and therefore the blood sugar was eliminated more quickly than normally (in particular, ZUNZ and LA BARRE (8)). This theory of the origin of the Staub effect became improbable when SOSKIN, ALLWEISS, and COHN (1934) found an i.v. Staub effect in a de-

pancreatized dog whose pancreas was compensated for by a constant infusion of insulin (9). It thus became clear that extra insulin was not needed for the occurrence of a Staub effect. Again, if the hypophysis is removed no Staub effect is obtained (SOSKIN ET AL. (10)). On these grounds SOSKIN and LEVINE (11) explained the Staub effect »as a progressive depression in the activity (production of the glycotropic or anti-insulin factor) of the anterior pituitary gland as a result of repeated or prolonged exposure to hyperglycemic levels. Thus, after several successive doses of sugar, the normal animal reaches that stage from which the hypophysectomized animal starts out.» In hypopituitarism an inverted Staub effect is usually obtained (12) which may be interpreted as some kind of an exhaustion phenomenon of the blood sugar relation.

In the same year (1934) HIMSWORTH (13) advanced a theory that the hyperglycaemia caused by the first dose activated the insulin in such a way that it had a stronger effect, although it was not present in surplus amounts. This »insulin kinase» was produced during the hyperglycaemia, most probably in the liver. Thus the difference between the two later theories is that while HIMSWORTH supposed the Staub effect to be caused by an activation of insulin, SOSKIN assumed it to be a result of a decrease in the inhibition of the insulin effect. In 1938 HIMSWORTH (14) also thought the inhibition theory the more probable.

Since contradictory results concerning the Staub effect have been obtained in children, and since as far as I know the i.v. Staub effect in children has not yet been investigated, I have deemed it advisable to consider this question.

The Staub Effect Following Intravenous Injection in Healthy Children

The intravenous injections were made in either the jugular or cubital vein. The duration of the injection was usually two to three minutes. The amount of glucose varied between 0.5 and 2 g per kg weight and it was usually given as a 10 % solution.

Table I

Intravenous Staub-Traugott effect in healthy children and adults.

Date	Case	Age (years)	Gluc./kg (g)	Interval (min.)	Fast. Val. (mg%)	Max.[1] (mg%)	Length[2] (min.)	Length I—Length II (min.)
14.9.—48	1 a	1 4/12	0.5	40	I 90	237	34	
					II	247	35	—1
16.9.—48	1 b	1 4/12	0.5	40	I 97	269	38	
					II	269	30	8
					III	232	40	—2 (I—III)
7.1.—49	13	1 11/12	0.5	60	I 79	233	29	
					II	228	27	2
11.8.—48	14	1	0.5	40	I 85	240	39	
					II	270	42	—3
4.3.—49	15	5	0.5	60	I 91	245	38	
					II	249	37	1
11.8.—48	16	1	0.5	40	I 85	223	29	
					II	225	29	0
11.2.—49	17	5	0.5	60	I 81	262	32	
					II	231	31	1
26.2.—49	15	5	0.5	105	I 85	253	40	
					II	215	38	2
18.9.—48	18	5	0.5	75	I 92	207	24	
					II	242	26	—2
23.2.—49	7	6	0.5	145	I 82	247	33	
					II	207	36	—3
22.2.—49	19	7	0.5	180	I 90	272	40	
					II	279	44	—4
11.3.—49	15	5	0.5	180	I 75	233	22	
					II	283	24	—2
1.3.—49	1 c	2	0.5	200	I 84	229	30	
					II	256	34	—4

[1] 3 minutes after injection.
[2] Falling time of the blood sugar to 0.1 %.

Table I (cont.)

Date	Case	Age (years)	Gluc./kg (g)	Interval (min.)	Fast. Val. (mg%)	Max.[1] (mg%)	Length[2] (min.)	Length I — Length II (min.)
9.3. —49	1 b	2	0.5	195	I 77	220	41	
					II	240	46	—5
21.12. —48	20	5	0.5	75	I 74	258	39	
					II	252	42	—3
25.2.— 49	1 a	2	0.5	190	I 79	236	29	
					II	263	34	—5
24.2. —49	15	5	0.5	200	I 95	274	36	
					II	273	44	—8
23.12. —48	1 c	2	0.5	150	I 83	286	33	
					II	245	37	—4
					III	248	37	—4 (I—III)
15.1. —49	21	3 6/12	1.0	105	I 83	386	40	
					II	361	51	—11
					III	361	60	—20 (I—III)
11.12. —48	1 b	2	1.6	105	I 85	542	51	
					II	400	69	—18
					III	590	82	—31 (I—III)
7.12. —48	1 a	2	2.0	90	I 82	600	65	
					II	452	72	—7
15.6. —49	22	20	0.3	75	I 105	227	58	
					II	240	48	10
2.10. —48	23	20	0.25	70	I 94	171	44	
					II	172	37	7
					III	165	34	10 (I—III)
8.6. —49	24	21	0.3	80	I 97	244	54	
					II	192	34	20
13.6. —49	25	24	0.3	80	I 107	238	46	
					II	230	37	7
17.6. —49	26	19	0.3	190	I 103	234	54	
					II	214	70	—16

[1] 3 minutes after injection.
[2] Falling time of the blood sugar to 0.1 %.

Fig. 1.

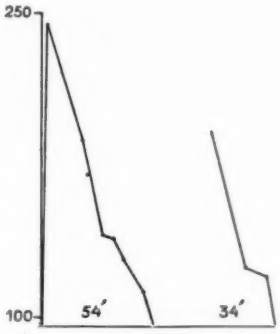

Fig. 2.

Fig. 1. Mean curves of 7 double tolerance tests on healthy children at intervals of from 40 to 60 minutes.

Fig. 2. Double tolerance test on adult (Case 21).

The interval between the injections varied from 40 to 200 minutes. The blood sugar was determined by the Hagedorn-Jensen micromethod. In all, twenty two such double and triple tolerance tests were performed on children from one to seven years of age (Table I). The table illustrates that the falling time of the blood sugar to 0.1 % was generally equally long in both tests, the interval being from 40 to 60 minutes. If the interval was prolonged over 60 minutes, the second curve usually fell more slowly than the first, which was also the case if the dose exceeded 0.5 g/kg. Fig. 1 shows the mean curves with 0.5 g/kg, the interval being 40—60 minutes. The time required for the blood sugar to fall to 0.1 per cent is 34 and 33 minutes. The maximal values in both curves are practically on the same level.

Thus the above-mentioned experiments did not at any rate yield any clear Staub effect in children, in contrast to adults, in whom, according to the literature and to my own experiments (Fig. 2), it was manifested except when the interval between injections was increased to three hours (Table I).

The Staub Effect by Mouth

Twenty double tolerance tests were performed on children between six months and seven years of age. The sugar was given as a 10 % solution, 2 g per kg weight on each occasion at intervals of two hours. Table II shows that the Staub effect usually set in, but there were also six obvious inverted reactions. It was at its strongest in those experiments where the maximal value of the first tolerance test was high and appears slight in those where the first maximum was below 130 mg%. This is consistent with the general opinion that the Staub effect is caused by the rise of the blood sugar level during the first tolerance test — whether it works through the hypophysis or the pancreas. But it seems on first sight to be in disagreement with the results published in a previous paper (24), according to which a peroral sugar dose stimulates the disappearance of intravenously injected glucose from blood the stronger, the less the blood sugar had risen in this peroral experiment. From these experiments the conclusion was drawn that the Staub effect was due not solely to the rise of blood sugar, but that during the absorption of sugar from the intestine something happened which caused an accelerated falling rate of the blood sugar — an increase of the minute volume of the liver or activation of insulin. The inconsistency is, however, only apparent, at least in part. It is known that the effect of insulin is stronger when the blood sugar level is high than when it is low. Very much more insulin would be required to lower the blood sugar from 160 to 150 mg% than from 130 to 120 mg% accordingly, the indicator showing the amount of active insulin (maximum of first curve minus maximum of second curve) is less sensitive the lower the curves are. Therefore it is probable that there is more active insulin present in the last experiments in Table II than is indicated by the degree of the Staub effect.

Another factor that in my opinion may contribute to the suppression of the »peroral» Staub effect when the first curve is low is the »Bahnung» phenomenon which is so common in physiology. If the capacity for absorption is disturbed during the night of fasting the second dose may be better absorbed than the

Table II

Peroral Staub-Traugott effect in healthy children.

Date	Case No.	Age (year)	Fast Val.	Max.		Max. I—Max. II (mg%)
				Curve I	Curve II	
				(mg%)		
15.12.—48	1 a[1]	1	87	169	128	41
22.11.—48	1 b	1	80	165	131	34
15.12.—48	1 b	1	87	164	134	30
27.10.—48	2	7	76	149	128	21
27.11.—48	1 a	1	93	148	138	10
11.1.—49	3	1 4/12	76	141	149	—8
6.4.—49	1 a	1 5/12	78	139	122	17
29.11.—49	1 c	1	83	139	133	6
9.4.—49	4	2 1/12	93	137	103	34
30.11.—49	5	1	93	131	105	26
29.11.—49	6	3	96	129	101	28
11.2.—49	7	6	81	129	134	—5
13.1.—49	8	1 5/12	62	128	126	2
17.1.—49	9	2 3/12	87	126	123	3
21.10.—49	10	9	84	125	128	—3
12.4.—49	11	6/12	95	124	121	3
8.4.—49	12	1 3/12	70	113	135	—22
17.1.—49	13	2	83	110	125	—15
11.4.—49	1 b	1 5/12	78	109	116	—7
7.4.—49	1 c	1 5/12	73	101	112	—11

[1] 1 a, 1 b, and 1 c are identical triplets.

first and cause as great or a greater rise in the blood sugar level, in spite of the catalyzation of the blood sugar regulation brought about by the first dose.

A third factor can also be imagined which might contribute to the suppression of the Staub effect. If the first tolerance test shows a low curve, having produced more of the blood sugar lowering factor, it is possible that this factor acts directly on other incretory glands (the hypophysis or the adrenal glands) in such a way that an antihormone (glycotropic factor or adrenalin)

Table III

Intravenous Staub-Traugott effect in coeliac disease.

Date	Case No. (Coeliacia patients)	Age (years)	Fast. Val. (mg%)	Max.[1] (mg%)	Length[2] (min.)	Length I—Length II (min.)
9.9.—48	1	6 3/12	107	I 242	34	
				II 228	40	—6
8.9.—48	2	2	69	I 236	32	
				II 222	28	4
1.9.—48	3	4 10/12	90	I 222	38	
				II 225	33	5
6.7.—48	4	3 7/12	76	I 228	36	
				II 266	40	—4
7.9.—48	5	4	86	I 233	29	
				II 247	26	3
3.9.—48	6	3	78	I 218	42	
				II 211	40	2
3.3.—49	7	10	91	I 224	33	
				II 229	32	1
2.3.—49	8	3 8/12	92	I 212	28	
				II 227	28	0

[1] 3 minutes after injection.
[2] Falling time of the blood sugar to 0.1 %.

is produced. Then it is possible that this anti-hormone dominates during the second tolerance test.

In experiments presented in the author's previous paper (23) (where the indicator showing the amount of active insulin brought about by the first peroral dose was the i.v. tolerance curve, and not the difference between the maximums of the peroral tolerance curves, as in the experiments in this paper), the two first disturbing factors were absent (the changes in the sensitivity of the indicators and the »Bahnung» of the absorption).

The anti-hormone of insulin could be present initially but

the high hyperglycaemia produced by the i.v. test, prevented its further secretion.

Therefore it can perhaps be understood why in the experiments presented above the Staub effect was not manifested when the curve was low, unlike those in which the i.v. tolerance test curve served as indicator.

One is tempted to test the way in which the Staub effect manifests itself in coeliac disease when the test is performed in the abovementioned way. It is known that the glucose tolerance test is usually low (FANCONI (15), THAYSEN (16), SVENSGAARD (17), GUY (18), CRAWFORD (19), ROSS (20), MACRAE and MORRIS (21), BADENOCH and MORRIS (22)). The most widely held opinion seems to be that this is due to absorption disturbance (ROSS, MACRAE and MORRIS, CRAWFORD, SVENSGAARD). According to others, the cause is either a primary or secondary disturbance of the blood sugar regulation (THAYSEN, BADENOCH and MORRIS). According to these latter, sensitivity to insulin is increased in coeliac disease; they assume that this is due to a decrease in the anti-insulin factor of the hypophysis. These authors were, in fact, able to obtain higher blood sugar curves in coeliac disease patients by injecting anterior lobe hormones. According to SOSKIN, if this is right an inverted Staub effect ought to be found in coeliac disease.

Table III shows eight i.v. double tolerance tests in coeliac disease patients. It may be noted that in some cases there was only a slight tendency towards the Staub effect. Thus these coeliac disease patients behave in this respect quite like healthy children.

Summary

Twenty one double i.v. glucose tolerance tests were performed on healthy children below seven years of age. The dose varied from 0.5 to 2 g per kg weight and the interval between the injections from 40 to 200 minutes. The first and second curves of the double tolerance tests were usually identical — the Staub-Traugott effect was not obtained. In the twenty double tolerance tests performed by the peroral route this effect was clearly obtained in

ten experiments. In four experiments the first and second curves reached approximately the same level, and in six there was clearly an inverted Staub-Traugott effect. Eight coeliac disease patients on whom i.v. tests were performed reacted to the Staub-Traugott effect in the same way as the healthy children.

Résumé

Vingt-et-un tests I.V. de double tolérance de glucose ont été effectués sur des enfants en parfait état de santé et au dessous de sept ans. Ces doses ont varié de 0.5 à 2 g par kg du poids et l'interval entre les injections de 40 à 200 minutes. La première et deuxième courbes du test de double tolérance étaient généralement identiques — l'effet de Staub-Traugott n'a pas été atteint. Sur les vingt tests de double tolérance effectués par la voie perorale, cet effet fut nettement atteint dans dix expériences. Dans quatre cas, la première et la deuxième courbes ont atteint approximativement le même niveau et, dans les six autres on a nettement constate un effet inverse de Staub-Traugott. Huit patients atteints de l'affection coeliaque sur qui les tests I.V. avaient été effectués ont réagi devant l'effet de Staub-Traugott comme les enfants bien portants.

Zusammenfassung

Bei gesunden Kindern unter 7 Jahren wurden 21 doppelte intravenöse Dextrose Belastungsproben durchgeführt. Die Dosis variierte von 0.5 bis 2 g pro kg Körpergewicht und die Zwischenzeit zwischen den Injektionen von 40 bis 200 Minuten. Die erste und die zweite Kurve der doppelten Belastungsprobe waren meistens identisch — der Staub-Traugott-Effekt war nicht hervorzubringen.

Bei 20 peroralen doppelten Belastungsproben war der Staub-Traugott-Effekt in 10 Fällen klar, in 4 Fällen stiegen die beiden Kurven ungefähr gleich hoch, und in 6 Fällen war die zweite Kurve bedeutend höher.

Bei 8 Patienten mit der Herter-Heubnerschen Krankheit verhielt sich die intravenöse doppelte Belastungsprobe wie bei gesunden Kindern.

Sumario

Se efectuaron 21 pruebas de tolerancia doble de glucosa I.V. en niños sanos de menos de 7 años de edad. La dosis varía entre 0.5 y 2 gramos por kilo de peso y el intervalo entre las inyecciones varía entre 40 y 200 minutos. Las primeras y segundas curvas de la prueba de tolerancia doble eran generalmente idénticas; no se obtuvo el efecto Staub-Traugott. En las 20 pruebas de tolerancia doble, efectuadas por vía peroral, se obtuvo claramente este efecto en diez experimentos. En cuatro experimentos las primeras y segundas curvas alcanzaron aproximadamente el mismo nivel y en seis apareció claramente un efecto invertido Staub-Traugott. Ocho enfermos de calíaca, en los cuales se effectuaron pruebas I.V., reaccionaron al efecto Staub-Traugott así como los niños sanos.

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FROM THE HOSPITAL FOR CONTAGIOUS DISEASES, STOCKHOLM.
CHIEF: DOCENT J. STRÖM.

Chronic Benign Granulocytopenia in a Child During the Second Year of Life

by

JUSTUS STRÖM

Recently SALOMONSEN in this journal reported a very interesting case of granulocytopenia lasting for more than one year. Referring to earlier observations by FANCONI, he felt justified in regarding chronic benign granulocytopenia as a new clinical entity.

The case I wish to report here was admitted to the Stockholm Hospital for Contagious Diseases in the summer of 1947 with a high fever and an eruption. The blood count revealed pronounced granulocytopenia which did not recede, and therefore I observed the patient for more than one year. The case will further elucidate the problem of chronic benign granulocytopenia in children and is therefore of both paediatric and haematologic interest, especially as it exhibited some symptoms not observed in the cases described earlier, particularly with regard to the skin symptoms.

Case Report

W.P., born April 7, 1946. Admitted July 24, 1947, aged one year and three months. Birth wt. 3 950 g. Breast-fed five months. Normal development. During the winter of 1947 repeated attacks of colds with a temperature of about 39° for a couple of days. Stayed in country for last seven weeks. No case of measles in surroundings.

Present Illness. Taken ill night of July 19, 1947. In morning 39°.3, no catarrhal symptoms. On 21st 39°.2—39°.7; on 22nd 39°.4—40°.3; on 23rd 36°.8—38°.1; on 24th 38°. On the night of 23rd an exanthema appeared, first on face, later also on neck and chest. Sulfonamides were administered during 21st and 22nd but had to be discontinued as the patient vomited. The inguinal lymph glands were swollen from the be-

ginning of the illness. Admitted to the hospital under the diagnosis: fever of uncertain cause + eruption.

Examination July 24: general condition good. Temp. 38°. Insignificant rhinitis, no cough. *Skin:* on face and behind the ears a confluent, large-patched exanthema. Scattered over trunk, arms, and thighs a macular eruption. *Fauces:* diffuse swelling and redness. No Koplik spots. *Lymph Glands:* pea-sized in the anguli mandibulae, pea-sized in the neck, grain-sized in the axillae, almost pea-sized in the inguae. *I.O.* normal. Spleen not palpable.

Blood: Hgb. 11.4 g%, RBC 5.1 mill., WBC 4 700. Unsegm. cells 1 %, segm. 0 %, monoc. 1 %, lymphoc. 96 %, plasma cells 2 %. Microsedimentation rate 8 mm/h.

The next day afebrile. Over entire body a maculo-papular grain to pea-sized exanthema, in parts confluent and pale red in colour. July 29 exanthema had disappeared. Aug. 1 some grain to pea-sized papulae on the arms and legs and some on the trunk. These disappeared after a few days. Microsedimentation rate Aug. 8 5 mm/h. Concerning the blood count see Table and Fig. *28.7: Bone Marrow:* very cell-rich specimen. Toxic alterations in the myelopoesis and marked left shift with a suggested arrest after the unsegmented cells. Erythropoesis normal. Megacaryocytes normal. Reticulum apparently hyperplastic. Rare cells of plasma cell type, all mononuclear. D.: granulocytopenia.

Discharged Aug. 2, 1947.

Readmitted Sept. 4, 1947.

According to the father there had been solitary eruptions or spots with varying localization and remaining for a couple of days during the entire stay at home. No itching.

Was taken ill on the evening of Sept. 3, 1947, with fever. During night eruption developed over entire body. According to the father, eruption very similar to previous one.

Examination Sept. 4: general condition good. Temp. 38°.4. *Skin:* on face, trunk, and extremities an extensive light red exanthema consisting of irregular maculo-papulous eruptions. *Fauces:* somewhat swollen. *Lymph Glands:* in neck and submandibularly some the size of a rather large pea. In axillae and inguae some grain-sized glands. *I.O.* normal. Spleen not palpable. Sept. 5 exanthema still present. Crust-covered ulceration on upper lip.

Blood: Hgb. 11.4 g%, RBC 5.2 mill., WBC 10100. Unsegm. cells 1 %, segm. 24 %, eos. 2 %, lymphoc. 73 %, thromboc. 222 000. Microsedimentation rate 10 mm/h.

Sept. 6. *Bone Marrow:* cell-rich specimen. Lively myelopoesis and erythropoesis without any signs of damage. Reticulum hyperplastic. Plasma cells normal. Megacaryocytosis normal. Moderate amount of

lymphocytes of various sizes — no lymphatic metaplasia. Specimen showed no specific change.

Sept. 9. Exanthema bleached.

Sept. 12. *Removal of Lymphatic Gland:* moderately hyperplastic lymphatic gland, showing slight oedema and hyperaemia. Rather abundant follicles and Fleming centra. No signs of systemic illness. Morbid anatomic diagnosis: slight non-specific reaction.

Course: afebrile after two days. Microsedimentation Sept. 11 5 mm/h; Sept. 18 6 mm/h. Blood count — see Table and Fig.

Discharged to home Sept. 20, 1947.

Readmitted Oct. 7, 1947.

After discharge the patient was well but tired. Then an eruption started on the right arm and began to develop more and more.

Examination Oct. 7: somewhat pale. Temp. 37°.3. *Fauces:* slightly reddened. *I.O.* normal. *Skin:* on right arm and forearm a number of crust-covered eruptions up to 1 cm large. On left arm several similar eruptions as well as on face and abdomen.

Microsedimentation rate 10 mm/h. Concerning the blood count see Table and Fig.

The impetigo healed rather rapidly.

I have since performed *follow up examinations* for one year. The patient was catarrhal with nasal catarrh, cough, and fever in Nov. 1947 and April and May 1948. Rather tired and complaining; failed to increase in weight. Weighed 12 500 g on Oct. 8, 1947, and 12 600 g on Nov. 25, 1948. Concerning blood count see Table and Fig.

Epicrisis. At the beginning of the illness, the appearance of the eruption and its character suggested measles. The absence of exposure and of catarrhal symptoms, however, as well as the blood count, contradicted this assumption. Exanthema subitum was also a possible diagnosis. However, the temperature had not returned to normal when the exanthema appeared, and the blood count showed only moderate leukopenia (4 700) and an unusually extreme lymphocytosis (96 %) even for a case of this disease. Later the patient developed localized spots that appeared and disappeared on the body. When the patient had a second exanthema similar to the first one after somewhat more than a month, the diagnosis exanthema subitum seemed still more improbable. After another month the patient developed a rather extensive impetigo and during the following year upper respiratory infections on three occasions. The lymph glands were somewhat enlarged generally.

Table

Date	Hgb. g%	RBC	WBC	Myel and Meta-myel	Un-segm.	Segm.	Gran. Total %	Eos.	Bas.	Mon.	Plasma Cells	Lym-phoc.	Total number of		Notes
													Gran.	Lymph.	
25.7	11.4	5.1	4 700		1	0	1			1	2	96	50	4 510	fever +
29.7			6 500	1	2	18	21	3		3		73	1 365	4 745	exanth.
31.7			6 000	1.5	1	9	11.5	3		3.5		82	690	4 920	
5.9	11.4	5.2	10 100	1	2	22	25	2				73	2 525	7 370	fever +
6.9			7 000		1	24	25	1		3		71	1 750	4 970	exanth.
8.9	10.7	4.4	6 100		2	11	13	2				85	790	5 185	
9.9			8 000		2	9	11	7		2		80	880	6 400	
15.9	11.8	4.4	9 800		1	13	14	2		5		79	1 370	7 740	
17.9	11.4	4.5	8 800			17	17	6		1		76	1 495	6 690	
8.10	10.8	4.3	16 000	2	5	34	41	6		5		48	6 560	7 680	impetigo
10.10	11.4	4.4	9 900	2	2	20	24	2	1	1		72	2 375	7 130	
14.10			8 300	2	2	19.5	23.5	2	1	4.5		69	1 950	5 725	
16.10			10 200	1	1	7.5	9.5	2.5		7.5		80.5	970	8 210	
15.12			8 800	2	1.5	16	19.5	2	0.5	2		76	1 710	6 690	
23.1	10.5	4.1	5 800	1	1	11	13	2.5		4.5		80	750	4 640	
1.3	10.7	3.8	6 100	1	2	24	27	2		4		67	1 645	4 090	
7.5	10.5	4.5	7 000		1	18	19	2		2		77	1 330	5 390	
22.5	11.1	4.5	6 900	1	4	21	26	1		4		69	1 790	4 760	
25.9	10.3	4.4	8 600	2	2	32	36	2.5		1.5		60	3 095	4 960	

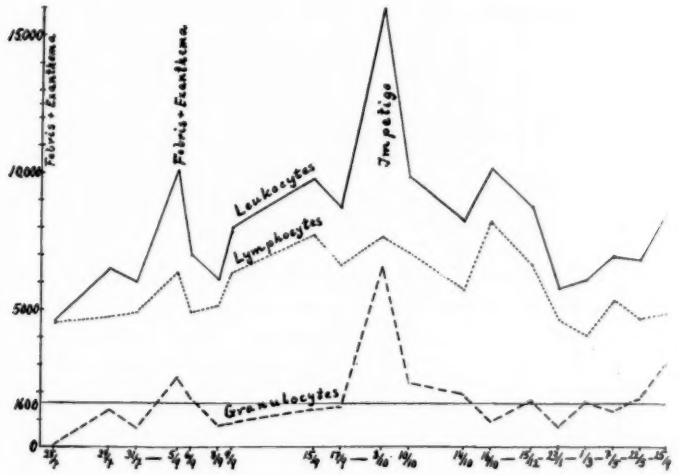

Figure.

The general condition of the patient over the fourteen-month observation period was rather good, even though he seemed tired and ill at ease, had a poor appetite, and consequently did not gain in weight. The constant characteristic feature of the disease, however, was the *differential white blood count*. The most striking feature was the marked *relative lymphocytosis,* which reached the extreme figure of 96 % at the first examination, at fourteen out of nineteen examinations was over 70 %, which is considered maximum for this age, and was 80 % or more on six occasions. However, there was also a certain tendency towards leukopenia; thus at nine examinations there were less than 8 000 white blood cells. When the absolute number of lymphocytes was calculated it proved to have exceeded 4 000 during the entire illness. It is true that the lymph glands were somewhat enlarged, but this seemed rather insignificant in the clinical picture. A removed lymph gland also showed a slight non-specific reaction.

The disturbance chiefly affected the *granulocytes*. In ten out of nineteen cases their relative amount was below the lower limit of 20 % and their absolute number was below 1 600 at nine exam-

inations. The lowest value was 50; on five further occasions it was below 1 000 (690, 750, 790, 880, and 970). Thus there was *in this case a marked tendency towards granulocytopenia for ten months.*

At the first examination (July 28) the *bone marrow* showed marked left shift with suggestion of an arrest after unsegmented cells, the diagnosis being granulocytopenia. On the second occasion (Sept. 6) there were no morbid alterations evident.

The *reaction* in the cellular composition of the peripheral blood *in later infections* on Sept. 5 and Oct. 8 showed that the number of neutrophile leukocytes had increased, most evidently the last time, thereafter returning to absolute values lower than 1 600 and remaining at this low value during non-infective periods.

Eosinophils were generally found in normal numbers, while the monocytes were on some occasions somewhat scarce. The thrombocytes were normal. The red blood cells showed normal conditions, as did the microsedimentation rate also.

Discussion

In 1941 FANCONI described a case of granulocytopenia in a seven month old child who was admitted to the hospital because of repeated infections which continued in the hospital at two-week intervals (angina, bronchitis etc.). At fourteen examinations the number of leukocytes exceeded 1 600 only three times and reached a minimum of 220. During and after the infections the granulocytopenia was more pronounced. Injections of nucleotides had no effect. The bone marrow showed an inhibition of the maturation of the granulocytes. In 1946 FANCONI gave a short report of another case in a seven month old child who for ten months showed »pronounced chronic granulocytopenia», but whose development in other respects was normal, the only symptoms being slight repeated infections. The bone marrow was normal in this case. Injections of Granulozytan produced fever and a rapidly receding increase in the granulocytes.

Quite recently (1948), SALOMONSEN gave a survey of granulocytopenias in children in this journal. In it he reported on an

interesting case of benign granulocytopenia. At the age of nine and a half months the child contracted a serious infection (pharyngitis + sinusitis) with high temperature over a period of three weeks. He was given a single large dose of sulfathiazole (2 g). The sedimentation rate was increased. The child was admitted to a paediatric hospital and the only positive findings were catarrhal symptoms and a pronounced granulocytopenia. The latter remained stationary for one and a half years and then gradually subsided. During this entire period there was a slight tendency towards leukopenia, marked relative lymphocytosis, relative monocytosis, and a great reduction in the neutrophile leukocytes, between 0 and 10 %, the absolute number of granulocytes varying between 0 and 500.

The bone marrow was examined twice and showed approximately normal conditions; only a slight tendency towards reduction in the number of mature granulocytes was observed.

The blood count was not affected by acute febrile upper respiratory infections during the granulocytopenia, whereas this was the case after the latter had disappeared. Nor did injections of pentnucleotide and liver extracts affect the blood count.

The patient presented constitutional defects. She was tired and had a poor appetite. There were repeated catarrhal infections with fever recurring about every two weeks, once stomatitis, and on one occasion a persistent furunculosis. As the granulocytopenia disappeared her condition improved and the infections ceased.

SALOMONSEN believes that the reason for the granulocytopenia was the infection. As to the pathogenesis, he considers that so far one can only guess. The bone marrow failed to reveal any definite pathological alterations. In his first case FANCONI encountered an inhibition of maturation to begin with, but also a picture that might be interpreted as phagocytosis of the neutrophils. In the other case the bone marrow was normal.

SALOMONSEN considers that this is a special disease, the characteristics of which are chronic marked selective granulocytopenia with a corresponding leukopenia, normal bone marrow, decreased resistance to infections, and an only slightly affected

general condition, not amenable to treatment with drugs used in granulocytopenias and resulting in spontaneous cure.

If my case be analyzed from these points of view, one finds that there was a marked granulocytopenia for a period of ten months. Further, the second condition, i.e. a normal bone marrow, was also fulfilled. A certain sensitivity to infections may also be noted. As a parallel to the furunculosis in SALOMONSEN's patient, the generalized impetigo may be advanced. It is noteworthy that an extensive, large-patched morbilliform exanthema appeared twice, and that spots appeared in various places in the interim. There was also slight affection of the general condition, with tiredness and poor appetite prevailing during the period of granulocytopenia. The child did not increase in weight during the ten months in question. The fourth point, the reaction on giving certain drugs affecting the granulocytes, was not tested, but it may be noted that there was a granulocyte reaction in infections, after which the granulocytes soon returned to the previous low level. The fifth point, i.e. spontaneous cure, may also be considered fulfilled by now.

Therefore I should like to interpret this case as one of chronic benign granulocytopenia, although of a somewhat less marked form than in SALOMONSEN's case. It resembles FANCONI's second case most closely; in this the sensitivity to infections was less and granulocytogenic drugs produced an increase in the granulocytes. The less serious character of my case is borne out by the less marked sensitivity to infections and a certain capacity on the part of the granulocytes to increase in number in the course of infections.

Clinically these cases are of great interest. They show that a marked peripheral granulocytopenia and even an agranulocytosis may exist for a long time in children, at least up to the age of two years, without serious symptoms. It is possible, however, that in these cases one should refrain from administering drugs affecting the granulocytopoesis. When there is a marked sensitivity to infections in infants and small children one should investigate whether a granulocytopenia is the underlying cause. This should also be done in protracted cases of furunculosis or

impetigo. Judging from my case, it is also possible that there may be a tendency for these children to develop exanthemas. If this should be so, the disease gains still greater importance, especially from the point of view of differential diagnosis.

Summary

A case is reported of a child who during its second year of life showed a pronounced granulocytopenia for a period of ten months. The illness started with an infection with a morbilliform exanthema, the granulocytes being reduced to 1 % (absolute number 50). A similar exanthema appeared again after about a month, spots having been disseminated on the skin all this time, and after still another month came a rather extensive impetigo. Otherwise the patient experienced only slight general symptoms, including tiredness, poor appetite, and a standstill in weight. There were also three more instances of catarrhal infections during the period of granulocytopenia.

The granulocytopenia appeared immediately after the infection and later during the symptom-free intervals. At nine of the nineteen examinations the absolute number was below the lower limit — 1 600 — and at six of these below 1 000, the lowest value being 50. However, the granulocytes increased in connection with infections. The bone marrow showed normal findings, broadly speaking. There was pronounced relative lymphocytosis. The lymph glands were somewhat enlarged but biopsy showed that there was only a slight non-specific reaction. The microsedimentation rate was normal.

The case can be considered as one of a new clinical entity, earlier described briefly by FANCONI and recently by SALOMONSEN as chronic benign granulocytopenia. Its somewhat lighter character was proved by the reaction of the granulocytes in infections and the less pronounced sensitiveness to infection. The morbilliform exanthema which appeared in this case during two febrile periods seems of special interest.

Résumé

Granulocytopénie bénigne chronique chez un enfant au cours de la seconde année

On fait mention d'un malade qui, au cours de sa seconde année, montra une granulocytopénie prononcée, pendant une période de 10 mois. La maladie débuta par une infection avec un exanthème morbilliforme, les granulocytes s'abaissant à 1 % (nombre absolu 50). Un exanthème semblable apparut à nouveau après un mois environ, se présentant alors sous forme de taches disséminées sur la peau, pendant toute cette époque — puis apparut encore, durant un autre mois, un impetigo assez étendu. A part cela, le patient ne présenta que quelques légers symptômes généraux, fatigue, manque d'appétit et poids stationnaire, outre trois poussées d'infection catarrhale durant la période de granulocytopénie.

La granulocytopénie apparut aussitôt après l'infection, et par la suite durant les intervalles libres de symptômes. A 9 des 19 examens, le nombre absolu était au dessous de la limite la plus basse — 1 600 — et à 6 de ces examens au dessous de 1 000, la valeur la plus basse étant 50. Toutefois, les granulocytes augmentèrent lors des infections. La moëlle osseuse présenta en général un aspect normal. Il y avait une lymphocytose relativement prononcée. Les ganglions lymphatiques furent quelque peu hypertrophiés, mais une biopsie montra qu'il n'y avait qu'une petite réaction non spécifique. La vitesse de micro sédimentation était normale.

Ce cas peut être considéré comme un cas de cette nouvelle entité clinique, précédemment décrite de façon brève par FANCONI, et récemment par SALOMONSEN, comme granulocytopénie bénigne et chronique. Son caractère de gravité moindre fut établi par la réaction granulocytaire lors des infections et par la sensibilité moins prononcée à l'infection. L'exanthème morbilliforme apparaissant à deux périodes fébriles semble d'intérêt particulier dans ce cas.

Zusammenfassung

Chronische benigne Granulocytopenie bei einem Kinde während seines zweiten Lebensjahres

Berichtung über einen Fall einer ausgesprochenen Granulocytopenie während des zweiten Lebensjahres unter einem Zeitraum von 10 Monaten. Die Krankheit begann mit einer Infektion, einem morbilliformen Ausschlag. Die Granulocyten wurden auf 1 % (absolute Anzahl 50) herabgesetzt. Ein ähnlicher Ausschlag trat wieder nach ungefähr einem Monat auf und nach einem weiteren Monat zeigte sich ein ziemlich ausgebreitetes Impetigo. Die allgemeinen Symptome waren leichte Müdigkeit, Appetitlosigkeit und stationäres Gewicht. Während der Dauer der Granulocytopenie traten noch drei weitere katarrhalische Infektionen auf.

Die Granulocytopenie trat sofort nach der Infektion in Erscheinung und später während symptomfreier Intervalle. Bei 9 von 19 Untersuchungen war die absolute Zahl unter der niedrigsten Grenze — 1 600 — und bei 6 von diesen unter 1 000; der niedrigste Wert war 50. Die Granulocyten nahmen jedoch bei den Infektionen zu. Das Knochenmark zeigte im allgemeinen ein normales Bild. Es herrschte eine ausgesprochene relative Lymphocytose. Die Lymphdrüsen waren ein wenig vergrössert, doch zeigte die Biopsie nur eine moderate nicht spezifische Reaktion. Die Mikrosenkungsreaktion war normal.

Dieser Fall gehört in einer neuen klinischen Einheit, die früher Fanconi kurz und vor kurzem Salomonsen als chronische benigne Granulocytopenie beschrieben haben. Ihr einigermassen leichter Charakter wurde durch die Reaktion der Granulocyten bei Infektionen bewiesen und durch die weniger ausgesprochene Empfindlichkeit gegen Infektionen. Von besonderem Interesse ist der morbilliforme Hautausschlag welcher in diesem Falle bei zwei Fieberperioden auftrat.

Sumario

Granulocitopenia cronica benigna en un niño durante su segundo año de vida

Se hace la relación de un caso que en el curso de su segundo año de vida presentó una pronunciada granulocitopenia por un período de 10 meses. La enfermedad se inició con un estado infeccioso y exantema morbiliforme, reduciendose los granulocitos a 1 % (numero absoluto 50). Un exantema similar apareció nuevamente al transcurrir aproximadamente un mes, existiendo maculas diseminadas sobre la piel durante todo este tiempo, luego de aun otro mes apareció un impétigo bastante extenso. Aparte de esto el enfermo solo experimentó leves sintomas generales, como ser anorrexia, decaimiento, y un estacionamiento del peso, y tuvo ademas tres procesos catarrales durante el período de granulocitopenia.

La granulocitopenia apareció inmediatamente después de la infección, y mas tarde durante los períodos asintomáticos. En 9 de los 19 examenes realizados el numero absoluto se encontraba por debajo del nivel — 1 600 — y en 6 por debajo de 1 000, el valor mas bajo fué de 50. De todas maneras se constató un aumento de los granulocitos durante los períodos infecciosos. Puede decirse, que los examenes de la medula osea eran normales. Existía una pronunciada linfocitósis relativa. Los ganglios linfáticos estaban algo aumentados de volumen, pero la biopsia demostró que existía solamente una leve reacción inespecífica. La velocidad de sedimentación era completamente normal.

Este caso puede considerarse como un caso dentro de la nueva entidad clinica, brevemente descrita anteriormente por FANCONI y recientemente por SALOMONSEN, como una granulocitopenia cronica benigna. Su caracter más leve o benigno se tradujo por una reacción granulocitica en el curso de las infecciones, y por una menor sensibilidad a la infección. De interes especial es el exantema morbiliforme que en este caso, apareció durante los dos períodos afebriles.

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FROM THE PAEDIATRIC DEPARTMENT OF THE CENTRAL HOSPITAL, BORÅS.
CHIEF: THE AUTHOR.

Some Present-Day Problems in Clinical Diabetes Research

by

BERTIL SÖDERLING, M.D.

Since the discovery and employment of insulin, no advance has been so important in the treatment of diabetes in children as the elimination of dietary restrictions. The way for this advance was paved by, among other things, the medley of dietary restrictions that had by then accumulated. Conservative forces had a braking effect on the freer development, however, and the clinical studies made by STOLTE[1] from 1927 on (publ. 1931) at Breslau Hospital passed unknown and unobserved. STOLTE's name was still unfamiliar until 1934, when SÖDERLING[1], who was about to publish his first series of cases of children treated without dietary restrictions, happened to read STOLTE's[1] paper. By this time the ground had been prepared, and as a result of the work of such researchers advocating unrestricted diet as LICHTENSTEIN (1935)[1], RÄIHÄ (1937)[1], SUNDAL (1937)[1], and BOJLÉN (1938)[1] dietary restrictions were gradually eliminated from treatment. The majority of diabetic children in the Northern countries were probably placed on free diet between the years 1934—38. LICHTENSTEIN interpreted the opinion of the therapeutists advocating unrestricted diet when he said that the elimination of dietary restrictions meant that we had finally fully realized the true meaning of the discovery of insulin and acted accordingly.

This change was a boon for the diabetic children and of much scientific interest. It afforded pregnant examples of the facts that problems relevant to metabolic disorders in diabetes cannot be solved as though they were purely mathematical propositions, and that the disease in question is dependent on too many

unknown factors to be controlled or explained by patent formulae alone. Values concerning the blood and urine sugar, the preferable carbohydrate consumption, and the so-called 'adequate amount of insulin' are not generally applicable. In one case reduction of hyperglycaemia, for example, may be advisable, while in another hyperglycaemia must be respected as a compensatory factor essential to the well-being of the patient. Often an increase in the carbohydrate consumption will not involve a proportionate or even absolute increase in the need for insulin. In some cases, on the other hand, an increased administration of insulin will often fail to produce a corresponding and desired reduction of the blood sugar. While one patient may react with a very considerable hyperglycaemia, but without becoming acidotic, another patient may, in spite of a rich carbohydrate intake and insulin, readily react with acidosis. When patients were placed on an unrestricted diet the role played by psychic factors became distinctly manifest. Finally, it became obvious that it was both safe and beneficial to give free play to the protective mechanism of the body and to the patient's appetite, whereby both hyperglycaemia and hypoglycaemia were gently balanced. The previously feared intercurrent diseases, for example, were reduced to more or less »ordinary» complications, no more serious than those that might befall any healthy individual.

The last fifteen years may be considered as forming the beginning of an epoch in which the therapeutist — pending the accumulation of further knowledge — adjusts his treatment according to the general well-being *(in every respect)* of the patient and the latter's ability to carry on his work. Above all, he does not aim at reducing the blood and urine sugar to normal, a procedure which does not always produce stable alleviation.

Even though on the whole we are still struggling against the same unknown factors as before, important results are being obtained, especially in the field of pathogenetic research, and it is hoped that although no immediate explanation can be expected, new light will soon be shed on the problem.

Much speaks in favour of diabetes mellitus' not being a pure insulin-deficiency disease. Its aetiology is still rather obscure.

The extremely complicated chemical processes which CORI & CORI[2], among others, have shown with the phosphorylation procedure suggest that a lack of necessary catalyzers may be the fundamental pathogenetic factor. Moreover, various kinds of catalyzers are hypothetically conceivable. In one case there may be a lack of antiacidotic substances, in another of antiinsulinary substances, and in a third a deficiency of antihyperglycaemic substances, with resultant predisposition to, respectively, acidosis, hypoglycaemia, and hyperglycaemia, etc. The investigation of HOUSSAY AND ASSOCIATES[3] of the part played by the pituitary gland in the carbohydrate metabolism, the increased knowledge of the homeostatic effect of the liver on the blood sugar, the interesting cases of diabetes with attendant enlargement of the liver, cholesterinaemia, and growth disorders[6], observations made in animal experiments with alloxan diabetes[5], the geographical distribution of diabetes, etc., are problems more or less intimately connected with the fundamental nature of the disease. As early as 1920 FALTA pointed out the individually different insulin-sensitivity of both insulin-sensitive and insulin-resistant diabetics.

With regard to his insulin-resistant cases, it should be mentioned that the adequate amount of insulin for pancreatectomized individuals (and animals) was found to be less than that of many a diabetic. While the latter may need up to 120 U insulin, the pancreatectomized individuals hitherto examined could manage on a daily dose of 26—40 U.[4]

The aetiology may also be viewed from the opposite angle — those needing but little insulin and exhibiting a paradoxical insulin sensitivity. A few paediatric cases from the diabetic clientele of Borås Hospital afford examples of this.

313/33. B. 1942, diabetes diagnosed 1944. Needed only 8 U; with this dosage urine at times completely sugar-free. Sometimes troublesome insulinism. Dec. 1946 admitted for observation *without* insulin. After a couple of days praecoma, acidosis, and blood sugar values of 454, 474 mg/100 cc.

1000/46. B. 1941, diabetes diagnosed 1946. 8 U; Retard ins., urine completely or almost sugar-free. Attempts to suspend insulinization six months later immediately increased the blood sugar to 406—422,

increased thirst. Acidosis did not occur during the four experimental days.

965/46. B. 1942, diabetes diagnosed 1946. 8 U sugar-free. Attempts seven months later to suspend this small dosage increased the blood sugar level to 320—348 with increased thirst and precipitant nocturnal urination. No acidosis during the short experiment.

989/47. B. 1944, diabetes diagnosed 1947. 2 U Retard — very slight or no urine sugar. Slight insulinism. Insulinization suspended a few days after three—four months' observation, whereupon acidosis and hyperglycaemia 364 occurred.

1/48. B. 1946, diabetes diagnosed 1948. 8 U — sugar-free, insulinism. Without insulin — thirst, hyperglycaemia 430—522, acidosis.

621/46. B. 1941, diabetes diagnosed 1946. During first year *40 U* Retard necessary; no traces of acidosis and about 30 g urine sugar per day. Now, 1948, *16 U* for same status.

684/46. B. 1939, diabetes diagnosed 1946. After needing rather heavy doses of insulin (40 U) with no acidosis and with about 50 g urine sugar per day for the first year, now sugar-free on *12 U* with insulinism. On the other hand, *without* insulin, thirst and hyperglycaemia.

The first four cases have two common characteristics, viz. (a) pathognomonically diabetes mellitus is clearly diagnosed, but (b) the patients' sensitivity to insulin is so considerable that it even exceeds that of normal children.

The last two cases show a very remarkable variation in their need of insulin without its being possible to trace the reasons therefor. An anatomical, definite defect in the parenchyma of the pancreas would hardly explain these variations.

Even though the aetiology is still an obscure problem, we must admit that we feel more and more inclined to believe that the administered insulin per se is *not always totally* but only partly responsible for the therapeutic effect. If a minimal dosage of 8—16 U insulin tolerable by a healthy child is able to produce sugar-free urine and insulinism in a diabetic, it seems improbable that this strong effect can be ascribed solely to the *quantity* of insulin administered. Perhaps the »healthy» insulin injected is more effective than the »morbid» (diabetic) in stimulating the production of catalyzers and thereby also the effect of the body's own insulin.

Summary

The author considers the discovery of insulin and the introduction of the free diet the most important practical advances in the treatment of diabetes in children. The free diet not only makes life more enjoyable for the children; its effect on the KH balance, among other things, has presumably revealed the erroneousness of many preconceived opinions.

Aetiologically the disease is still very obscure in spite of experimental research in cases of extirpation of the pancreas and alloxan diabetes and in spite of promising discoveries by Cori & Cori, Houssay, and others. Diabetic cases with noteworthy insulin sensitivity, even higher than in healthy persons, or cases in which the need of insulin suddenly becomes greatly reduced are of aetiological interest. Seven cases are described. In many cases diabetes mellitus in children does not appear to be a pure insulin deficiency disease.

Résumé

L'auteur considère la découverte de l'insuline et l'introduction du régime libre comme les progrès expérimentaux les plus importants dans le traitement du diabète chez les enfants. Non seulement le régime libre rend la vie plus agréable aux enfants, mais sa répercussion sur la balance HC, entre autres, a probablement démontré la fausseté de bien des opinions préconçues.

Etiologiquement, la maladie est encore très obscure, malgré les recherches expérimentales dans certains cas d'ablation du pancréas et de diabète dû à l'alloxan, et en dépit de découvertes prometteuses faites par Cori & Cori, Houssay, et d'autres. Les cas de diabète présentant une sensibilité remarquable à l'insuline, sensibilité même plus grande que chez des sujets normaux, ou les cas dans lesquels le besoin d'insuline s'abaisse subitement de façon considérable, sont d'un intérêt étiologique. On a décrit sept cas. Dans bien des cas, le diabète sucré chez les enfants ne semble pas être une simple déficience de la sécrétion d'insuline.

Zusammenfassung

Verfasser betrachtet die Insulinentdeckung und die Einführung der freien Kost als praktisch wichtigste Fortschritte in der Behandlung von Kindern mit Diabetes mellitus. Die freie Kost macht nicht nur das Leben der Kinder glücklicher, ihre Wirkung auf den Stoffwechsel hat die früher irrtümliche Kohlehydrateinstellung durchaus verändert.

Die Ätiologie der Krankheit ist noch sehr im Dunkel trotz der experimentellen wissenschaftlichen Untersuchungen mit Pankreasextirpation und Alloxan-Diabetes und trotz der vielversprechenden Entdeckung von CORI und CORI, HOUSSAY u. a.

Zu erwähnen sind Diabetesfälle mit grösserer Empfindlichkeit für Insulin als bei gesunden Personen. Ätiologisch interessant sind auch Fälle bei welchen der Insulinbedarf plötzlich herabgesetzt wurde. Sieben Fälle sind beschrieben. In manchen Fällen von Kinder-Diabetes scheint es sich nicht um eine Krankheit zu handeln, sondern um Insulinmangel.

Sumario

El autor considera como el adelanto practico mas importante en el tratamiento de la diabetes del niño, el descubrimiento de la insulina y la introducción de la dieta libre. La dieta libre no solamente hace la vida más agradable a los niños. Sus efectos sobre el balance de los hidratos de carbono entre otras cosas, ha probablemente revelado el error de muchas opiniones preconcebidas. Etiologicamente la enfermedad es todavia muy oscura, a pesar de los trabajos experimentales sobre la extirpación del pancras y de la diabetis por el alloxan y a pesar de los descubrimientos prometedores de CORI y CORI, HOUSSAY, y otros. Los casos de diabetis con una remarcable sensibilidad a la insulina, aun mayor que en la personas normales, y los caos en que el requerimiento de insulina se reduce repentinamente enormenente, son de gran interes etiologico. Se describen 7 casos. En muchos casos la diabetis mellitus en el nino no se presenta como una enfermedad por deficiencia insulinica pura.

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(3) —— p. 121.
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Die Methoden der Wertbestimmung des normalen und pathologischen Wachstums im Kindes- und Jugendalter[1]

von

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Das Wachstum bildet ein biologisches Phänomen, dessen innerste Ursache unserer Nachforschung entgeht. Wir können es jedoch abschätzen, indem wir die Veränderungen in der Struktur, Zusammensetzung, Dimensionen und Proportionen des Körpers, im Laufe des Entwicklungsalters analysieren.

Aber auch diese Abschätzung ist nicht so einfach, wie es auf den ersten Blick erscheinen kann, da wir bei unserm Studium, sofort bemerkenswerten Schwierigkeiten begegnen. Die erste und die vielleicht wichtigste von diesen Schwierigkeiten besteht in der Feststellung, welche Einheiten als Wachstumseinheiten definiert werden können. Der Körper ist ein Kaleidoskop, welches sich fortwährend unter unseren Augen verwandelt, nicht nur was die Form und die Proportionen betrifft, sondern auch in dem was die Struktur und chemische Zusammensetzung angeht. Und diese fortschreitenden Veränderungen des Somas sind so tief, dass eine gegebene Zuwachseinheit eine vollständig verschiedene Tatsache darstellt, je nachdem ob man sie in einem Entwicklungsstadium oder in einem darauffolgenden Stadium betrachtet.

Um ein Beispiel anzuführen, bei einem Säugling bedeutet die Gewichtzunahme von 1 kg, eine Zunahme der Gehirnsubstanz und der Eingeweide; bei einem Jüngling wird sie hauptsächlich einer Zunahme von Knochensubstanz und Muskelmassen entsprechen; bei einem Erwachsenen hingegen wird sie nur eine Fettanhäufung

[1] Vortrag gehalten den 16. Sept. 1948 in Zürich (Schweizer. Akad. der mediz. Wissenschaften, Italienisch-schweizerische medizinische Tagung).

als Reservelager bedeuten. Natürlich kann man die nötigen Unterschiede nur dank einer sehr genauen Analyse und einem quantitativen Studium der einzelnen Organe, der einzelnen Teile und der einzelnen Segmente des Körpers, während der aufeinanderfolgenden Wachstums- und Entwicklungsphasen feststellen. Diese Richtung wurde in Italien besonders von Viola, Castaldi und von ihren Schülern verfolgt. Andere Autoren haben diese quantitative Untersuchungsmethode noch weiter ausgedehnt, indem sie sie bei der Veränderungen der mikroskopischen Struktur anwandten; unter diesem Gesichtspunkt klassisch sind die Untersuchungen von Hammar und seinen Mitarbeitern über das involutive Strukturphänomen des Thymus. Andere Autoren, endlich, haben vorgezogen, die verschiedenen Phasen des Wachstums und der Entwicklung zu verfolgen, indem sie die fortschreitenden Veränderungen, welche die chemischen Bestandteile des Somas quantitativ erleiden, studierten. Aber es handelt sich hierbei um alles andere als eine leichte Untersuchung, welche daher bis heute nur sehr teilweise durchgeführt werden konnte.

Wenn auch diese verschiedenen Untersuchungstechniken wichtige Ergebnisse für unser Wissen um das Entwicklungsalter erbracht haben, so lösen sie dennoch nicht das Problem welche Einheit zu wählen ist, um das Wachstum des menschlichen Körpers abzuschätzen.

Mit diesen Beschränkungen, können wir jedoch immerhin das Studium des menschlichen Wachstums unternehmen, indem wir drei von den hauptsächlichsten Arten der Untersuchungstechniken dabei verwenden.

Die erste Technik beruht auf dem figurativen, ikastischen Prinzip, und besteht in der Reproduktion der verschiedenen Wachstumsphasen mit Hilfe von Zeichnungen oder Photographien. Die Methode ist ausführlich besonders von Stratz und von Bauer in Deutschland, und von Pende und seinen Schülern in Italien angewandt worden. Sie verdient weiterhin angewandt zu werden, da die figurative Reproduktion des Körpers erlaubt viele Angaben zu sammeln, welche auch den genauesten Messungen sonst entgehen würden. Die figurative Methode erzeigt sich unersetzlich vorteilhaft um jene Wachstumsphasen zu verfolgen, bei

welchen das Material quantitativ gering ist (Embryologie), oder wenn die Messung sich als schwierig erweist, oder endlich wenn die Veränderungen derartig kompliziert sind, dass die rein numerisch ausdruckbaren Masse, nicht genügen um eine vollständige Vorstellung von ihren verworrenen Beziehungen, zu geben. Das Ungünstige bei dieser Technik zum Studium des Wachstums besteht darin, dass sie eher erklärend als beschreibend ist, und da sie nicht auf Angaben von genauen Feststellungen beruht, gibt sie Anlass zu verschiedenen individuellen Deutungen.

Man versteht darum, weshalb von dem grössten Teil der Autoren, welche sich mit menschlicher Auxologie befassten, der Vorzug der zweiten Studiumstechnik gegeben wurde, welche sich auf die Sammlung der möglichst grossen Anzahl von Massen und Bewertungsangaben gründet, die erhaltenen Resultate in Tabellen vereinigt, und sie zur grösseren Bequemlichkeit und Anschaulichkeit häufig vermittels Zeichnungen darstellt. Diese Methode ist bekanntlich von Quételet eingeweiht worden. Er mass das Gewicht, die Länge und die äusseren Dimensionen lebender menschlicher Organismen in der verschiedenen Wachstumsphasen und dehnte seine Untersuchungen auch bis zu den Messungen einiger innerer Organe bei Leichen aus, Richtung welche später Vierordt, Oppenheimer, Castaldi und Vannucci verfolgten. Gleichzeitig entwickelte sich die Ausarbeitung der gesammelten Angaben, mittels der besten Statistikmethoden.

Wir werden nun kurz die dritte Untersuchungstechnik, welche man bei den auxologischen Forschungen verwenden kann, betrachten; diese Technik, welche wir als eine »analytische» bezeichnen können, hat sich unlängst den beiden vorher erwähnten angeschlossen und besteht darin, den Wachstums-phänomen vermittels des analytischen und mathematischen Symbolismus, Ausdruck zu verleihen. Diese symbolischen Verbindungen können ihrerseits von rationellen Ausdrücken gebildet werden oder ausschliesslich von rein empirischen Grundlagen ausgehen. Wie es auch immer sei, es ist unzweifelhalt dass die analytischen Methoden des Wachstumsstudiums den grossen Vorteil gegenüber den Photographien, Tabellen und Zeichnungen haben, dass sie eine grössere Einfachheit, Kürze, Präzision und Stabilität aufweisen.

Ausser diesen Eigenschaften, müssen wir jedoch noch einen anderen sehr wichtigen Vorteil erwähnen: dank der Annahme analytischer Ausdrücke, können wir die Berechnung in das Studium der auxologischen Phänomen einführen.

Wenn wir die erste Technik überspringen, welche einen reinen figurativen Charakter hat und daher von den Messungen absehen kann (obwohl dieselben, im allgemeinen beigefügt werden und von der photographischen Reproduktion des Somas einen höheren Wert erhalten), so sehen wir dass sowohl die zweite als auch die dritte unter den auxologischen Untersuchungstechniken, welche wir bisher erwähnten, sich auf die Sammlung einer verschiedenen Anzahl von Massen, Anzeichen, und Abschätzungssystemen mannigfaltiger Art basieren.

In Nordamerika, wo die auxometrischen Forschungen in diesen letzten Jahren eine immer grössere Bedeutung angenommen haben, hat man verschiedene Methoden vorgeschlagen um das Wachstum und die Entwicklung der Kinder zusammen mit ihrem allgemeinen Körperzustand bewerten zu können. Neuerdings (1946) ist es zu einem Übereinkommen gekommen, zwischen den Zentren der Wachstumserforschung der Universität Harvard von Boston und der Universität von Iowa, welche zweifellos diejenigen sind, welche auf diesem Gebiet die grösste Autorität besitzen. Auf diese Weise haben Stuart und Meredith, welche die beiden soeben erwähnten Zentren leiten ein Programm formulieren können, dessen Einführung in allen amerikanischen Schulen vorgeschlagen wurde. Die auxometrische Methode von Stuart und Meredith erlaubt Erkundigungen zu bekommen nicht nur in Bezug auf das Wachstum, sondern auch auf die Entwicklung und den Ernährungszustand. Die gewählten Messungen sind auf das Mindeste beschränkt, und aufweisen keine technische Schwierigkeit, die den allgemeinen Gebrauch verhindern könnte. Die Methode gestattet uns, über die Länge und Masse des Somas, wie auch über den Betrag der drei hauptsächlichsten Körpergewebe, welche seine Masse ausmachen (Skelett, Muskulatur, Fettpolster) möglichst genau zu orientieren.

Es wird interessieren, wenn wir die Hauptrichtlinien dieses Programmes prüfend betrachten. Zuerst muss man, wie üblich,

die Körperlänge messen, welche ohne Zweifel das beste Mass darstellt, über welches wir verfügen können, um die lineare Grösse eines Individuums zu schätzen, und um ihre Variationen während des Entwicklungsalters kennen zu lernen. Zweitens wird das Gewicht gemessen, um die allgemeine Masse des Körpers und das Wachstum der Masse im Laufe der Zeit zu schätzen. Bis jetzt nichts Besonderes, weil seit langer Zeit, Länge und Gewicht zum Zwecke der Abschätzung des Wachstums gedient haben. Wie aber Stuart und Meredith richtig bemerken, ist es wichtig zu erkennen, wenn man z. B. ein übermässiges Gewicht, in Verhältnis zum Alter und zur Länge vorfindet, ob dasselbe dem Vorhandensein umfangreicher, massiver Knochen, oder einer übermässig entwickelten Muskulatur, oder eines überflüssigen Fettpolsters zuzuschreiben ist, oder aber ob alle diese drei Faktoren proportionell anormal sind. Es ist daher ersichtlich, dass die Feststellung des Gewichtes und der Länge von additionalen Messungen und Abschätzungen ergänzt werden muss.

Was die Entwicklung des Skeletts betrifft, Stuart und Meredith auf die radiologische Untersuchung verzichten (wegen der Kosten und der technischen Schwierigkeiten) und beschränken sich, als additionale Messungen, den Brustumfang und die Beckenbreite vorzuschlagen. Was die Muskulatur angeht, so kann man, nach Stuart und Meredith, eine gute Abschätzung erhalten, wenn man den grössten Umfang des Beines in Höhe der Wade misst. Was endlich die Abschätzung des Fettpolsters betrifft, wird sie bestens nur klinisch durchgeführt und vermittels des bekannten pentavalenten Systems eingeschrieben.

Hiermit verzichten Stuart und Meredith auf die sehr genaue, aber teuere, radiologische Fettpolsteruntersuchung, deren Technik in diesen letzten Jahren gründlich bearbeitet wurde.

Ich weise auf die Originalveröffentlichung der amerikanischen Autoren hin, was die technischen Einzelheiten betrifft, mit welchen es möglich ist, eine Standardisierung dieser Messungen zu erhalten. Daselbst finden sich, sei es in Form von Tabellen, sei es in Graphiken ausgedrückt, die Werte der fünf fundamentalen Masse, mit ihren Progressionen vom Alter von fünf Jahren bis zu dem von 18 Jahren, sei es beim Manne oder Weibe. Die Werte

sind nicht nur als Durchschnittswerte sondern auch mit den prozentualen Veränderungen, ausgedrückt.

An dieser Stelle, wegen Zeitmangels, soll ich verzichten selbst auf eine kurze Illustrierung dieser sogenannten »Prozentualmethode», die so grosse Bedeutung und Verbreitung bei den auxometrischen Studien, besonders in Nordamerika erhalten hat. Ich erwähne nur dass Faber (1929) hat sich das Verdienst errungen die Neuerung vorgeschlagen zu haben, welche darin besteht nicht nur das Durchschnittsgewicht und die Durchschnittlänge für jede einzelne Altersstufe anzugeben, sondern auch die Verteilung dieser Werte, je nach ihrer prozentualen Häufigkeit. Man erhält, auf diese Weise, viele Veränderlichkeitszonen an Stelle der üblichen Durchsnittskurven.

Zweifellos ist diese Methode nicht exakt wie jene der Standard-Abweichung, welche vorzugsweise von den italienischen Konstitutionsforschern (Viola, Pende, Berghinz, Schiassi, Benedetti) angewandt wurde. Wir müssen jedoch hervorheben, dass die äusserste Genauigkeit dieser letzten Methode notwendig ist um den konstitutionellen Typus eines gegebenen Individuums zu definieren, aber dass sie in der Auxologie überflüssig erscheint, da wir uns hier Massen gegenüber befinden, welche fortwährend variieren, in Funktion der Zeit. Wie sich von selbst ergibt, ist es auch natürlich für einen Arzt leichter, sich mit der Prozentsatz-Methode vertreut zu machen, als mit derjenigen der sigmatischen Abweichung, welche Quadraterhebungen und Quadratwurzeln erfordert. Jedenfalls möchte ich daran erinnern dass Jackson und Kelly Graphiken ausgearbeitet haben, dank welcher es möglich ist die individuellen Veränderungen, während des Wachstums, sowohl vermittels der Prozentsätze als auch vermittels der sigmatischen Abweichung, auszudrücken.

Eine grosse Verbreitung hat neulich in Amerika die Wertbestimmungsmethode des Wachstums gehabt, welche von Wetzel vorgeschlagen wurde; es handelt sich um eine Graphik in Form eines Flechtgitters, welche gerade deshalb unter den Namen »Wetzel'sches Gitter» (»Wetzel Grid») bekannt ist. Diese Graphik geht von mathematischen Prinzipien aus, welche wir hier überspringen müssen; sie erlaubt auf Grund der Länge- bzw. Ge-

wichtmessung, Angaben über die Merkmale der Körperbildung und der Geschwindigkeit der somatischen Entwicklung. Der Vorzug des Wetzel'schen Gitters besteht nicht nur in der Tatsache dass es gestattet die Normalität des somatischen Wachstums, dank des einfachen Gegenüberstellens von Länge und Gewicht, festzustellen, sondern auch in der Möglichkeit gleichzeitig, dank der erhaltenen Angaben, auch den Entwicklungsgrad, den Ernährungsgrad, die Grundproduktion von Wärme und den Kalorienbedarf zu erkennen.

Die Wetzel'sche Methode hat Beifall gefunden von Seite berühmter Wachstumsforschern (Brody, Breckenridge und Vincent); es hat jedoch nicht an Einwänden gefehlt (Stuart u. Meredith, Mann, Dreizen und Spies) und viele Autoren behaupten dass es notwendig ist, mit weiteren Messungen und Abschätzungen die schon ziemlich komplizierte Methode zu ergänzen.

Dank der obengenannten Methoden, seien sie mehr oder weniger kompliziert, können wir ziemlich gut über das Wachstum und den Ernährungs-zustand der Individuen orientiert sein. Was aber die wirkliche eigentlich Entwicklung angeht, ist zweifelhaft ob man vermittels der vorherangeführten Methoden zu wirklich zuverlässigen Resultaten gelangen kann.

Es wurde versucht Abschätzungsnormen der Körperentwicklung zu erlangen, mittels der Bestimmung der Lebensfähigkeit und der Zahnentwicklung; aber es steht ausser Frage dass nur die radiologische Untersuchung der Knochen, wenn sie methodisch und systematisch durchgeführt wird, uns eine genaue Darstellung der Entwicklungsphasen von der ersten Kindheit bis zur Reife, geben kann. Die notwendige Technik, wie bekannt, schon standardisiert ist, und sie hat von Seite des »Growth and Development Committee» (White House Conference. 1932) ihre höchste Billigung erhalten. Die Wichtigkeit dieses radiologischen Studiums wird klar, wenn man bedenkt dass damit es möglich ist, mit der Zwischenzeiten eines Semesters, die Phasen der Knochenreife in der Individuen beiderlei Geschlechts, von Geburt bis zum achtzehnten Lebensjahre, verfolgen. Zur Abschätzung der Knochenentwicklung mittels dieser Methode, sind aber zehn Röntgenaufnahmen notwendig; billiger ist dagegen die Methode welche

von Vogt und Vickers vorgeschlagen wurde, bei der nur zwei Röntgenaufnahmen genügen; sie erlaubt aber nur die Knochenentwicklung in den ersten sechs Lebensjahren festzustellen.

Von einem anderen Gesichtspunkt ist Todd ausgegangen; seine Methode stützt sich auf der radiologischen Untersuchung der Hand und auf der darauffolgenden Feststellung der Veränderungen, welche von den Gelenksoberflächen der Knochen und den epiphysärischen Knorpeln dargestellt werden. Todd geht damit von der Beobachtung der Knochenform aus. Nach seiner Ansicht, jede Gelenkverbindung, um zur Reife zu gelangen, muss notwendigerweise eine Serie von vorübergehenden Übergängen durchmachen, welche als Zeiger der Skelettentwicklung angenommen werden. Todd hat auch eine Graphik vorgeschlagen, welche die Durchschnittswerte des Reifens des Skeletts für jedes Alter ausdrückt. Sehr nützlicherweise kann diese Methode, mit dem Gebrauch der sogenannten roten Graphik (»red graph method») welche neuerdings von Pyle und Mitarbeitern vorgeschlagen wurde, eine Ergänzung finden. In dieser Graphik fügt man dem nach Todd's Prinzip erhaltenen Durchschnittswert, die Altersgleichwertigkeiten der Gelenkoberfläche, welche sich im meist zurückgebliebenen Stadium und bzw. im meist fortgeschrittenen Entwicklungsalter befindet hinzu. Auf diese Weise gesellt sich zu den linearen Graphik des Todd, eine andere von zonenmässigem Aussehen. Wir möchten nun zuletzt noch sagen, dass dank der Arbeit von Mann (und Mitarbeitern) eine interessante Gegenüberstellung der Angaben, welche die Gittermethode von Wetzel bietet, mit denen welche man vermittels der Skelettbewertung nach Todd und nach der soeben erwähnten »roten Graphik» erhalten kann, möglich ist. Der gleichzeitige Gebrauch der beiden Forschungsmethoden kann eine Aufklärung auf dem Gebiet der Beziehungen zwischen der Knochenentwicklung und derjenigen der Weichteile erbringen.

Ohne irgendwie die Vorzüge leugnen zu wollen, welche in der von Wetzel vorgeschlagenen Gittermethode enthalten sind, ganz besonders wenn dieselbe von anderen obenerwähnten Abschätzungen, ergänzt wird, so glaube ich dennoch dass dieselbe nicht allgemein in praktischen Gebrauch genommen werden kann, son-

dern dass sie hauptsächlich in spezialisierten auxologischen Zentren angewandt werden kann.

Mir scheint hingegen, dass zum Zwecke der schnellen Orientierung der Schulärzte, der Lehrer und der Familien über die Modalitäten nach welchen das Wachstum eines Kindes erfolgt, die von mir jüngst (1946) vorgeschlagene Methode der auxologischen Klassifikation weit besser geeignet ist. In meiner Klassifikation habe ich mich auf die Werte der Länge und des Gewichts basiert, und auf ihren respektiven Unterschied (in Jahren und Monaten bewertet) in Hinsicht der normalen Werte für das respektive Alter und für das respektive Geschlecht. Das Wachstum, so denke ich, kann als regelmässig angesehen werden, wenn die Unterschiede des Gewichts und der Länge nicht die Grenze eines Jahres erreichen (sei es mehr, sei es weniger) im Vergleich mit dem normalen Altersdurchschnitt. Ich bezeichne dieses normalen Wachstum mit dem Namen: »Typosomie.» Wenn dagegen der Überschuss oder der Mangel mehr ersichtlich ist, obgleich er sich in massvollen Grenzen hält (das heisst mit einem Unterschied in mehr oder weniger von einem bis zu drei Jahren im Vergleich mit der Norm) so spreche ich von unregelmässigem Wachstum (»Disauxìa»); dabei haben wir acht möglichen Abweichungen: Hypersomie (parallelen staturalen und ponderalen Überschuss), Hyposomie (parallelen staturalen und ponderalen Mangel), Makrosomie (isolierten staturalen Überschuss), Mikrosomie (isolierten staturalen Mangel), Pachysomie (isolierten ponderalen Überschuss), Leptosomie (isolierten ponderalen Mangel), Makroleptosomie (staturalen Überschuss mit ponderalen Mangel) und endlich Mikropachysomie (staturalen Mangel mit ponderalen Überschuss).

Wenn die Länge und das Gewicht stark überschüssig oder mangelhaft sind (mit einem Unterschied, sei es in mehr oder weniger, über drei Jahre hinaus), so sprechen wir von pathologischen Wachstumsformen (Auxopathien) und dann haben wir Riesenwuchs, Zwergwuchs, Fettsucht oder Kachexien, einfacher oder verschiedenartig zusammengestellter Art. Es handelt sich, wie man sieht, von Bezeichnungen leichter ethymologischer Bedeutung, weshalb, wenn man den Unterschied festgestellt hat, es

möglich ist, ohne irgendwelche mnemonischen Kunststücke, das zu untersuchende Individuum in der respektiven auxologischen Gruppe unterzubringen. Natürlich erleichtern eine Tabelle und eine sehr einfach zu handhabende Graphik, noch ausserdem die Aufgabe.

Vor kurzem hat Gobessi eine nützliche graphische Anwendung der von mir vorgebrachten Klassifikation erdacht, und hat sie mit dem Namen »auxometrisches Dreieck» bezeichnet. Es handelt sich um ein System von Cartesianischen Koordinaten auf welchen, auf die vertikale Achse der Ordinaten die Ausschüsse der Länge (sei es in mehr oder weniger) eingezeichnet werden, während auf die horizontale Achse der Aszissen, die Ausschüsse des Gewichts, ebenfalls in mehr oder weniger, angegeben werden. Die Linie welche den Nullwert der Ausschüsse der Statur mit der Null der ponderalen verbindet, bildet auf diese Art die Hypothenuse eines rechteckigen Dreiecks, welches der perfekten. Normalität des Wachstums entspricht. Es ist klar dass je nach den Unterschieden, in mehr oder weniger, sei es der Länge, sei es des Gewichts, die Hypothenuse dieses Dreiecks differieren wird. Die vertikale Kathete, mit ihren Veränderungen, ruft leicht die Veränderungen der Körperlänge ins Gedächtnis, während die horizontale Kathete leicht die Idee der »Breite», der »Korpulenz» des Individuums gibt. Auf diese Weise, mit Hilfe dieser einfachen bidimensionalen geometrischen Figur, kann man die aufeinanderfolgenden Veränderungen eines Individuums, während der Phasen seines staturalen und ponderalen Wachstums verfolgen.

Die von mir vorgeschlagene Klassifikation, macht natürlich nicht den Anspruch perfekt zu sein und bietet, was das Studium des Wachstums betrifft, dieselben Übelstände, welche die Methoden haben, die sich nur auf die Bestimmung der Länge und des Gewichts basieren, und hier können wir auch die schon erwähnte komplizierte Gittermethode Wetzels miteinschliessen. Wie dem auch ist, wie neulich Tatafiore bemerkte, meine äusserst einfache Klassifikationsmethode erlaubt nicht nur mit genügender Elastizität die Grenzen zwischen normalem und anormalem Wachstum zu liefern, sondern auch die hauptsächlichsten Syndrome veränderten und pathologischen Wachstums zu identifizieren und unterscheiden.

Zusammenfassung

Die Erforschung des menschlichen Wachstums kann mittels drei verschiedener Hauptmethoden verfolgt werden. Die erste Methode gründet sich auf die bildliche Vorstellung; die zweite auf die Sammlung mancher Masse und Indices, welche man nachher in Tabellen und Zeichnungen vereinen und darstellen kann; die dritte, endlich, auf die Erfindung von analytischen und mathematischen Symbolen.

Eine kurze Erklärung solcher Methoden, welche besonders im Nord-Amerika zwecks der Wertbestimmung des menschlichen Wachstums angewandt wurden, wird nun vom Verfasser angegeben. Ein besonderes Interesse verdienen die Methoden, welche sich auf einfache Masse gründen, die nachher mittels des prozentischen Systems verteilt werden können. Die Methode der fünf Grundmasse, nach Stuart und Meredith, und das Flechtwerk nach Wetzel, sowie die radiologische Methode nach Todd, werden kurz erwähnt. Endlich bespricht Verfasser eine sehr einfache persönliche Methode, welche mittels der Gewichts- bzw. Höhenbestimmung, die Erreichung einer auxologischen Klassifikation erlaubt, damit nicht nur der Arzt, sondern auch der Laie leicht und bald über die Gangart des somatischen Wachstums während des ganzen Entwicklungsalters orientiert wird.

Summary

The growth of man can be investigated in three ways. The first method is based upon visual impression. According to the second method various measurements are collected which subsequently are evaluated in tables and figures. The third method finally deals with analytical and mathematical symbols.

The author briefly discussed methods which are used particularly in North America in the investigation of the growth of man. Of particular interest are those methods based upon simple measurements which subsequently can be evaluated in percentage according to certain systems. The method of the five basic measurements according to Stuart and Meredith, the system of Wetzel, and the radiological system of Todd are briefly discussed. Finally, the author discussed a very simple method of his own, according to

which the weight and height can be classified in an »auxological» system. A physician and also a lay person can by means of this method easily follow the physical growth during the whole stage of development.

Résumé

La croissance de l'homme peut être déterminée de trois manières. La première méthode est basée sur l'impression visuelle. Suivant la deuxième méthode, plusieurs mesurages sont effectués qui sont ensuite évalués sous forme de tableaux et de dessins. La troisième méthode, finalement, emploie des symboles analytiques et mathématiques.

L'auteur a discuté brièvement les méthodes employées en particulier en Amérique du Nord dans l'étude sur la croissance de l'homme. D'un intérêt particulier sont les méthodes basées sur de simples mesurages qui peuvent être ensuite évalués en pourcentage, conformément à certains systèmes. La méthode de cinq mesurages de base selon Stuart et Meredith, le système de Wetzel et le système radiologique de Todd font l'objet d'une courte discussion. Finalement, l'auteur discutait une méthode très simple, pratiquée par lui-même, suivant laquelle le poids et la taille peuvent être classés d'après un système »auxologique». Un médecin et même une personne n'ayant pas de qualifications spéciales peuvent facilement suivre, par cette méthode, la croissance physique pendant toute la durée du développement.

Sumario

Se puede seguir el estudio del crecimiento humano por medio de tres distintos métodos capitales. El primero se basa en representaciones gráficas, el segundo en la compilación de muchas materias e índices, que después se pueden purificar y exponer en cuadros y dibujos; el tercero, finalmente, se basa en el invento de los símbolos analíticos y matemáticos.

El autor da una corta explicación de estos distintos métodos, los cuales se usaron en EE. UU. para la valoración del crecimiento humano. Los métodos dignos de especial interés se basan en material sencillas, las cuales después se pueden distribuir por el

sistema del tanto por ciento. Se mencionan brevemente las cinco materias fundamentales según Stuart y Meredith, el tejido según Wetzel y el método radiológico según Todd. Finalmente el autor describe un método muy sencillo y personal que, mediante la determinación del peso y de la altura permite una clasificación auxológica, de manera que tanto el médico como el dilettante pueden orientarse de una manera fácil y rápida sobre la marcha del crecimiento somático durante todos los años de crecimiento.

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FROM THE PAEDIATRIC CLINIC OF KAROLINSKA INSTITUTET AT THE NORRTULL HOSPITAL, STOCKHOLM.
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Migraine of Early Onset

A Study of Thirty One Cases in Which the Disease First Appeared Between One and Four Years of Age

by

Bo VAHLQUIST and GUNNAR HACKZELL

Migraine may appear during the first years of life. The presence of subjective signs, such as headache and flimmer scotoma, is often difficult to determine in young children. The true nature of the symptoms frequently remains obscure for years.

In connection with investigations of the frequency and nature of the migraine syndrome in various age groups (VAHLQUIST AND ASSOCIATES 1949), we have assembled a series of thirty one cases in which the first symptoms of migraine appeared between the ages of one and four years. Eighteen of them were found in connection with the investigations cited above. The remainder were observed in the wards or outpatient departments of the paediatric clinics of Stockholm and Uppsala and registered in the hospital records under the diagnosis migraine or cephalalgia.[1] Our criteria for the diagnosis of migraine were attacks of headache separated by intervals with no symptoms whatever, as well as at least two of the following four symptoms: nausea, flimmer scotoma, hemicrania, and hereditary predisposition.

A brief survey of the thirty one cases fulfilling the foregoing criteria is given in Table 1.

Typical Case Reports

Case 1. Ch. W., boy born 1940. Diagnosis: migraine. First signs developed at one year of age. Examined 1947.

[1] We are indebted to Professors Lichtenstein and Malmberg in Stockholm and Professor Gyllenswärd in Uppsala, who permitted us to study the case records of patients with migraine at the respective paediatric clinics.

There was a history of typical migraine for several generations in the mother's family. The mother's symptoms first appeared after the patient's birth. The attacks were generally associated with menstruation. They disappeared during a subsequent pregnancy, but returned with menses. There was right-sided pain with a pronounced sensation of seasickness which necessitated remaining in bed even when the pain was not excessively severe.

The patient was delivered with forceps. His birth weight was 2 930 g. He had erysipelas at the age of two weeks. When he was ten months old he was badly frightened by an air-raid siren, and after that had abnormal fear reactions and suffered from pavor nocturnus. There was mild acidosis in connection with acute infections, but never severe vomiting. Feverish conditions were not accompanied by headache. His mental development was above the average. He had urticaria in connection with an infection but otherwise no allergic manifestations.

The first typical attack occurred at the age of one year. He suddenly turned pale and later had an attack of violent vomiting. During the next two years he had several attacks a week, always of the same type. Occasionally he had them when he was out and had to be carried home. When he was about three he began to complain of pain in his head during the attacks. There was no definite flimmer scotoma or vertigo but usually bradycardia ranging down to 40 and 50. The attacks generally ended in a heavy sleep. Between the attacks he was perfectly healthy and very active. The attacks always came late in the day without any apparent exciting cause. His mother, who is a physician, had never observed any hypersensitivity to particular foodstuffs. During the six months preceding examination he had only three attacks. Physical examination revealed nothing of interest. The heart was normal. Skin tests with various allergens gave completely negative results.

Comment: This is a case of severe migraine in which the first attacks appeared at the age of one year. The bradycardia noted in connection with the attacks might possibly suggest temporary cerebral oedema with allergic background. However, the mother, a physician, had never observed any connection with ingestion of a specific food. Skin tests with about forty extracts at the age of six years gave completely negative results.

Case 7. A.P., boy born 1940. Diagnosis: migraine. The first symptoms made their appearance at the age of two years and a half. The patient was first examined in 1944. There was no family history of migraine. The patient had never been ill except for the attacks described in the following.

Since the age of approximately two and a half years he had had

Table 1.

Migraine of early onset. Symptom picture in 31 cases in which disease appeared between ages of 1 and 4 years.

No.	Pat.	Sex	Age at Onset	Age at Examination	Maximum Incidence	Tendency	Cyclic Vomiting	First Definitely[1] Established Headache Years	Exciting Factor
1	C. W.	♂	1	6	1 or 2 weekly	decreas.	0	3	0
2	J. C.	♂	1	18	1 in 2 mos	»	0	—	fatigue, sunlight
3	U. B.	♂	2	10	1 weekly	»	0	2	psych. phys. exert., movies
4	C. G.	♂	2	10	1 or 2 monthly	»	0	2	excitement, movies
5	R. W.	♀	2	11	—	»	0	2	movies, fatigue
6	M. S.	♀	2	5	1 weekly	unchang.	0	2½	phys. exert.
7	A. P.	♂	2	4	1 in 3 mos	»	0	2½	
8	L. N.	♂	2	7	1 monthly	»	0	2½	fatigue, cold excit. psych.
9	G. P.	♂	2	19	1 »	decreas.	+	3	excit., fatigue
10	K. E. K.	♂	2	28	2 »	»	+	4	sunlight, obstip.
11	G. Å.	♂	2	16	1 weekly	»	0	4—5	phys. or psych. exert., salty food
12	S. S.	♂	3	6	1 »	unchang.	+	3	—
13	V. B.	♀	3	11	2 »	decreas.	0	3	phys. exert., car and train travel
14	O. N.	♂	3	20	2 monthly	»	0	3	fatigue
15	P. P.	♂	3	10	1 or 2 weekly	increas.	0	3	nervousness, fatigue
16	T. A.	♂	3	16	2 »	decreas.	0	3	examin. movies, fatigue
17	J. Ö.	♂	3	11	2 monthly	»	0	3—4	movies, phys. psych. exert.
18	B. L.	♂	3	15	1 weekly	»	0	4	emotion, psych. exert.
19	O. K.	♂	3	11	1 in 3 mos	»	0	4	emotion, hunger
20	B. K.	♂	4	21	2 monthly	disappear.	0	4	0
21	P. O. S.	♂	4	13	1 »	decreas.	0	4	movies, emotion
22	B. R.	♀	4	11	1 weekly	—	0	4	arithmetic, movies, heat
23	L. S.	♀	4	11	2 »	decreas.	0	4	late nights, fatigue, movies
24	G. A.	♀	4	11	2 monthly	»	0	4	overwork, movies, sunlight
25	B. A.	♂	4	11	2 »	»	0	4	phys. psych. exert.
26	K. G. A.	♂	4	11	1 »	»	0	4	phys. psych. exert., hunger
27	J. A. B.	♂	4	11	1 weekly	»	0	4	0
28	H. E.	♂	4	10	2 monthly	»	0	4	oppressive weather
29	E. P.	♂	4	20	2 »	unchang.	0	4	fatigue
30	M. W.	♀	4	17	1 weekly	increas.	0	4	fatigue
31	G. F.	♀	4	20	1 »	unchang.	0	4	late nights
	Mean		3 yrs	11 yrs			3/31		

[1] In the smallest children in particular, the attacks were recognized by the vomiting and pallor only. Not until they were older was headache reported.

No.	Symptom Picture							Comments
	Duration	Intensity	Unilateral Headache	Nausea	Flimmer	Vertigo	Heredity[2]	
1	2—3 hrs	severe	+	+		0	+	mother a physician
2	1—3 »	»	+	+	+		+	
3	—	»	0	+	+	+	+	during attacks at age of about 2 years, pat. wanted to press head against cold window
4	4—5 hrs	»	+	+	+	+	0	
5	1 hour	»	0	+	+		+	
6	2—6 hrs	»	0	+		0	0	
7	1—2 »	»	+	+		+	0	hosp. at 4 yrs. D: migraine
8	4—6 »	»	0	+		0	+	
9	12 »	»	0	+		0	(+)	hosp. at 7 yrs. D: cycl. vomit.
10	4—24 »	»	+	+	+		+	hosp. at 3 yrs. D: cycl. vomit.
11	2—3 »	»	0	+		0	+	hospitalized at 12 yrs. D: migraine
12	2—3 »	»	+	+		0	(+)	
13	24 »	»	0	+	+		+	hospitalized at 7 yrs. D: migraine
14	2 »	»	+	+	+		(+)	father a physician
15	2—12 »	»	+	+		0	+	
16	2—3 »	»	+	+		0	+	
17	2—3 »	»	+	+		0	(+)	hospitalized at 8 yrs. D: migraine
18	3—12 »	»	+	+	+		+	hospitalized at 11 yrs. D: cephalalgia (migraine)
19	2—3 »	»	+	+		0	(+)	hosp. at 5 yrs. D: migraine
20	1 hour	»	0	+		0	+	hosp. at 9 yrs. D: migraine
21	2—3 hrs	»	0	+		0	+	hosp. at 9 yrs. D: migraine
22	2—3 »	»	+	+		0	(+)	
23	2—3 »	»	+	+		0	0	
24	1 d.	»	0	+	+		+	
25	2 hrs—2 d.	»	0	+		0	+	father and mother migraine
26	1—2 hrs	»	+	+		0	+	
27	½—2 d.	»	0	+		+	(+)	
28	1—2 »	»	0	+		0	+	
29	3—12 hrs	»	+	+	+	+	+	
30	—	»	+	+	+		+	
31	3—4 d.	»	+	+	+	+	+	
	2½ hrs		18/31	31/31	12/31	6/31	20/31	

[2] + Indicates migraine in parents or siblings.
(+) Indicates migraine in grandparents or parents' siblings.

about eight attacks of sudden headache in the left side of his forehead, usually associated with nausea and sometimes ending with vomiting. The attacks lasted for an hour or two, after which the patient fell asleep. When he woke up an hour or two later he was as bright as usual. One attack was accompanied by pronounced vertigo. The attacks usually appeared when the patient was fatigued or cold. He was a bright and cheerful child of normal mental development. The eye grounds were normal. The patient exhibited certain anomalies, including an abnormally short left index and an asymmetrical thorax.

Comment: This is a case of typical migraine of early onset in a boy with some minor constitutional anomalies. The family history does not contain any mention of migraine. The attacks generally appeared when he was tired or cold. One of the most recent attacks was accompanied by pronounced vertigo.

Case 12. S.S., boy born 1937. Diagnosis: migraine and cyclic vomiting. The first attack occurred at the age of three years. The patient was examined in 1943. Neither of the parents had headache, but a maternal aunt had had typical migraine since her thirties.

Since the age of three years the patient had been having attacks of »pain in the right eye» followed by violent vomiting about once a week. During the attack he was »pale green» and had photophobia. The bilious vomiting which concluded the attacks sometimes lasted a couple of hours. In addition to these attacks, the boy repeatedly had attacks of violent vomiting lasting for one or two days without any headache. Physical examination revealed nothing of note. There were no refractive errors, and the eye grounds were normal.

Comment: This boy, who was six years old at the examination, had attacks of typical migraineous character from the age of three on. The alternating attacks of persistent vomiting without obvious cause for as long as two days at a time seemingly justify the diagnosis of cyclic vomiting.

Case 14. O.N., boy born 1928. Diagnosis: migraine. The first symptoms appeared at the age of three years. The patient was given a follow-up in 1948. Neither of the parents had migraine, but typical migraine had appeared for several generations in the mother's family.

During the first attack, at the age of three, the patient turned pale, complained of pain in his forehead, wanted to lie down, and finally vomited. In the years that followed, the attacks gradually increased to one or two monthly. The pain across the forehead was preceded by flimmer scotoma and followed by vomiting and sleep. After puberty the

attacks decreased in frequency, and at the time of examination the boy was having only one or two a year. They usually developed in the afternoon. At first a visit to the movies or a train trip almost invariably brought on an attack, but he also had numerous attacks for no apparent reason. In later years, an incipient attack could be staved off with a Saridon tablet administered as soon as the first signs appeared.

Comment: Like Case 7, this patient is the child of a physician and has been under careful supervision. The attacks, which began at the age of three, were typical. Visits to the moving pictures brought them on so regularly that the patient gave up going to them for several years. The conditions improved appreciably after puberty.

Case 20. B.K., boy born 1925. Diagnosis: migraine. The first attack occurred at the age of four years. The patient was given a follow-up examination in 1946.

One of the patient's brothers had typical migraine and also eczema. The tendency was present in the mother's family.

The patient was somewhat allergic, with urticaria from chocolate etc. During the first years of his life he often complained of abdominal pains. He had his attacks of headache between four and fourteen years of age, with as many as two attacks a month in the preschool period. The symptoms were as follows: severe pain in the forehead, sensitivity to noise, nausea, and vomiting. The patient always fell asleep at the end of the attacks.

Comment: This is one of the rare cases in which the parents had no idea of any factors precipitating the attacks. The patient's family showed parallel tendencies to migraine and allergy. The last attack occurred at the age of fourteen years. The patient had been free from the condition for seven years at the time of the after-examination. A detailed allergic study could not be made.

Symptom Picture

The ages of the patients in the present study ranged from four to twenty eight years, the median age being eleven. Twenty three of the thirty one patients were males.

The following facts are worthy of note. The earliest age at which any of the children mentioned headache or »pain in one eye» was two years, but even before that many of them had suffered attacks when they had to be put to bed because of sudden

pallor, nausea, and violent vomiting. In one case (No. 1) the mother, who was a physician and herself suffered from migraine, noted several of these attacks when the child was only one year old.

The attacks of migraine were invariably so severe that they caused the patient to stay in bed. Most of them lasted only a few hours, but in some of the cases the relatives reported a duration of twelve to forty-eight hours. The median duration for the whole group was two and a half hours. In many cases the attacks were followed by profound sleep from which the children awoke fully recovered.

Severe vertigo in association with the headache was observed in one patient (No. 7) at the age of four. Five other patients reported vertigo in connection with the attacks. (According to VAN BOGAERT AND ASSOCIATES [1928] and ATKINSON [1943], some forms of Menière's disease represent an equivalent of migraine.) Initial flimmer scotoma was present in twelve out of thirty one patients at after-examination. It is our experience that this symptom, too, may be present and clearly described in the preschool age.

The attacks of headache were associated with nausea in all the patients and culminated in vomiting in most of them. In three children (Nos. 9, 10, and 12) the vomiting was so intense and prolonged that it was diagnosed as of acetonemic origin. (A discussion of the relation between migraine of early onset and cyclic vomiting will be found in a paper by VAHLQUIST, 1949.) The children often complained of abdominal pain in connection with the vomiting, but reports of colic between the attacks were not particularly common.

The frequency of the attacks varied widely. The figures given in Table 1 refer to the periods of most severe symptoms and range from twice weekly to once quarterly. In twenty out of thirty cases, at least one of the parents or siblings had typical migraine and in seven others the condition was present in one or more of the parents' siblings or the grandparents. The authors found a migraine incidence of 13.3 % in a normal series of women whose average age was forty years, as compared with

38.7 % in the mothers of the children with migraine under discussion. The difference is statistically probable, 25.4 ± 9.1 %. More than half the patients showed distinct signs of »neurolability» (WALLGREN). Both these and the remainder reported psychic factors (nervous tension, visits to the moving pictures, tiredness, etc.) as the commonest causes of the attacks of headache.

The prognosis for these migraine cases of early onset does not appear to be especially unfavourable. The frequency of the attacks was said to be diminishing in twenty out of twenty two patients who had passed the age of seven years. One of the patients who was over fifteen years had been completely free from symptoms for seven years, and four of the remaining ten had at most three or four attacks a year.

The Incidence of Migraine of Early Onset in the Offspring of Families With Severe Migraine in One or Other of the Parents

The more recent a disease is and the more interested the parents are in it, the easier it is to secure complete and reliable information regarding the nature of the complaint. Migraine has a highly hereditary character. We considered it advisable to try to collect a series of families in which either husband or wife had migraine and to study the children of such parents.

Through the kindness of Professor Antoni, the head of the Neurological Clinic of *Serafimerlasarettet*, we were able to contact a number of migraine cases treated as outpatients at that hospital during the last few years. We chose only those which fitted our definition of migraine as set out in the introduction to the present paper. As a rule the cases chosen were severe. The great majority, or twenty three out of twenty six, of the patients who reported for examination were women. The results of this investigation with regard to the incidence of migraine in the offspring are shown in Table 2.

Of forty three children from twenty six families in which one of the parents had pronounced migraine, only three, a boy of seven and two girls of eleven, exhibited distinct symptoms of the same affection. In none of the others had the parents observed any

Table 2.

Incidence of migraine in children of families in which one or other of parents had same disease.

Parents With Typical Migraine		No. of Families	Children		
♂	♀		Total	Mean Age	Typical Migraine
3	23	26	43	7 yrs (4 mos—27 yrs)	3

suspicious attacks, despite the fact that many of the mothers, some of them with a history of migraine for several generations, had studied their children carefully in order to find out if they had inherited the tendency.

No outstandingly characteristic features could be noted in the children in these migraine families. Quite a few, it is true, showed evidence of nervous instability, but the frequency of such signs is rather high in the average population, too. One or two of the children generally had abdominal cramp when nervous. In none of the cases did the history provide evidence of cyclic vomiting.

Discussion

French physicians in particular have been interested in migraine in early childhood (Fabre 1904; Comby 1927; Debré and Broca 1935). Diagnosis is not always easy at that age and many physicians are not aware that the disease occurs in young children. In addition, the symptoms are more difficult to evaluate than in older patients. Attacks of nausea and vomiting occur in children more often from other causes, e.g. infections. The headache is less pronounced than the nausea in some cases. The child finds it difficult to give a clear picture of other symptoms, particularly the flimmer scotoma that is so often helpful in the diagnosis of older patients.

Consequently a wrong diagnosis may easily be made, partic-

ularly at the beginning of the disease before the relatives are aware of its transitory and recurrent nature. Such misinterpretation may even lead to surgical intervention due to suspected abdominal disease or neoplasm of the brain.

Of the thirty one cases reported in Table 1, twenty three were males. This figure does not justify the conclusion that migraine in early childhood is more common and/or more severe in boys than girls, since the material is a selected one and too small to permit conclusions. In the aforementioned investigation by VAHLQUIST AND ASSOCIATES, fifty five migraine cases were found among 1 236 schoolchildren between the ages of ten and twelve; twenty nine were boys and twenty six girls. Thirteen of the boys and eleven of the girls had their first attacks before they reached six years of age.

The symptom picture of migraine attacks at an early age does not differ essentially from that of older children or adults. Even in the preschool years the headache and the nausea may sometimes be supplemented by typical flimmer scotoma, vertigo, and the like. But in some respect there are undeniable differences. The prodromal signs, if any, are often of very short duration. A child may suddenly stop playing and lie down with headache and signs of nausea. After an hour or two of severe pain and vomiting the signs slowly recede and a refreshing sleep ensues. A transient rise in temperature may accompany the attack in children with especially intense symptoms.

A study of the factors that bring on attacks of migraine in children suggests that the psychogenic element is exceedingly important. The majority of the children were said by their parents to be sensitive, nervous, and of uneven disposition, with various behaviour disturbances such as nail-biting. They had their attacks when they were fatigued following exciting experiences. Insufficient sleep and irregular meals may also help to bring on an attack.

Visits to the moving pictures are included among the predisposing factors surprisingly often (eight out of thirty one); in some of the cases the attacks were said to occur in this connection only. The element of exitement probably acts together with fatigue,

intense visual impressions, and a stuffy atmosphere. Later, in the school years, tests and examinations became stumbling blocks. Not a few youngsters had failed important examinations due to an attack of migraine.

The theory that allergic factors are of decisive importance in producing attacks of migraine has found many advocates in the United States (VAUGHAN 1927; BALYEAT and RINKEL 1931; HARTSOCK and MCGURL 1938). There is no doubt that attacks of headache of migraine type can be brought on in this way. We have had patients who have stated definitely that the predisposing factor was the ingestion of pork, mayonnaise, etc. However, our experiences gained from thorough allergic analyses of forty patients (HACKZELL AND ASSOCIATES 1949), most of them adults, with typical migraine do not bear out the theory that an allergic background is commonly found in Sweden. Our standpoint in this respect is shared by numerous other workers of recent years (VALLERY-RADOT 1935, PALMER 1946, WOLFF 1947; in Sweden, BERGQUIST 1948). When certain American workers report a therapeutic effect from desensitization or elimination diet in as high as 80 %, is should be borne in mind that comparable results have been presented by ophthalmologists following correction of refractive errors (GRUNERT 1938) and likewise by other specialists following a series of widely varying methods (cf. O'SULLIVAN 1939).

The result of our study of the children in families in which one of the parents had migraine was to some extent surprising. Of forty three children, not more than three exhibited definite migraine. However, the average age in this material was relatively low — seven years. Probably a study of the same children when they were older would have given a different result. In a series published by ALLAN (1932), not less than 61 % of the offspring of families in which either the father or the mother had migraine also exhibited the disease. However, ALLAN also reported the incidence of migraine among physicians' families in Mecklenburg County, North Carolina, U.S.A., to be as high as 54 % for men and 53 % for women. In any case, it is clear that

severe migraine in a mother or father does not necessarily reappear as migraine of especially early onset in the children.

The treatment of migraine in the preschool years is essentially prophylactic. Due to the rather abrupt onset of the attacks, with early signs of nausea, oral administration of analgetics usually proves to be ineffective. Gynergen injections should be restricted to those rather infrequent cases with intense symptoms lasting for many hours. In some children we have observed that this form of medication has a satisfactory effect on the headache but intensifies the nausea following.

The prophylactic measures aim to eliminate the factors bringing on the attacks. The parents should be informed about the unfavourable influence of tension and fatigue. Moving pictures, parties, or journeys may be just as inappropriate for these children as irregular meals and insufficient sleep. In many cases the tense atmosphere in a family with threatening divorce or other conflict situations, e.g. in school, may constitute the precipitating factor for recurrent attacks. Migraine is definitely a psychosomatic disease, particularly in childhood and adolescence, and intelligent analysis along these lines is of paramount importance for good therapeutic results. Administration of tablets of Bellergal or Moloid for several weeks may prove a useful supplement to this therapy.

Summary

The authors report on thirty one cases of migraine with onset between one and four years of age. Headache was not given as a symptom before the age of two years, but attacks of paleness and intense vomiting sometimes set in at the age of only one year. The attacks are generally shorter, the prodromal signs are less marked, and the nausea is more intense in children than in adults. At the time of the follow-up study the frequency of the attacks was as a rule diminishing. Consequently the prognosis does not seem too unfavourable in the cases with early onset.

In twenty six families with severe migraine in one or another of the parents, only three out of forty three children (average age seven years) manifested signs of the same disease.

Therefore it would seem that migraine in one or other of the parents does not necessarily bring about early onset of the disease in the offspring.

Résumé

Migraines apparaissant précocement. Étude de 31 cas où les symptômes apparaissent entre 1 et 4 ans

Les auteurs font un rapport sur 31 cas de migraine débutant entre 1 et 4 ans.

Le mal de tête n'est pas cité comme symptôme avant l'âge de deux ans, mais des attaques de pâleur et de forts vomissements commencent parfois à l'âge d'un an seulement.

Les attaques sont généralement plus courtes, les prodromes moins marqués mais la nausée plus forte chez les enfants que chez les adultes. Lors de la poursuite de cette étude, la fréquence des attaques allait, en général, en diminuant. Le pronostic ne semble, par conséquent, pas trop défavorable dans les cas d'attaques précoces.

Sur 26 familles dans lesquelles l'un ou l'autre des parents souffrait de migraine grave, trois enfants seulement sur 43 (âge moyen 7 ans) manifestèrent des signes d'affection semblable. Ainsi semblerait-il que la migraine de l'un ou l'autre des parents n'entraîne pas nécessairement des attaques précoces de ce mal chez l'enfant.

Zusammenfassung

Früher Auftreten von Migräne. Eine Untersuchung von 31 Fällen beim ersten Auftreten der Erkrankung im Alter von 1 bis 4 Jahren

Die Verfasser berichten über 31 Fälle von Migräne, mit Beginn im Alter von 1 bis 4 Jahren. Bei Kindern unter 2 Jahren wurde Kopfschmerz nicht als Symptom angegeben, sondern manchmal trat schon im Alter von bloss einem Jahr anfallsweise schweres Erbrechen und Blässe ein. Die Anfälle sind gewöhnlich kürzer, die prodromalen Symptomen weniger ausgesprochen, aber die Nausea ist bei Kindern intensiver als bei Erwachsenen. Während der Zeit der fortgesetzten Beobachtung nahm die

Häufigkeit der Anfälle in der Regel ab. Infolgedessen scheint bei Fällen von frühem Auftreten die Prognose nicht allzu ungünstig zu sein.

In 26 Familien, in denen der eine oder andere Elternteil an schwerer Migräne litt, haben sich nur bei 3 Kindern von 43 (durchschnittliches Alter 7 Jahre) Zeichen derselben Krankheit gezeigt. Deshalb könnte man annehmen, dass Migräne bei dem einen oder anderen Elternteil nicht notwendigerweise einen frühen Ausbruch der Krankheit bei der Nachkommenschaft bedingt.

Sumario

Migrena de comienzo precoz. Un estudio sobre 31 casos donde la enfermedad hace su primera aparición a la edad de 1 a 4 años

Los autores informan sobre 31 casos de migrena que comienzan a la edad de 1 a 4 años. La cefalea no constituyo un sintoma antes de los dos años de edad, pero accesos de palidez intensa y vomitos comenzaron ya a la edad de un año. Los accesos son generalmente cortos, los sintomas prodromicos menos marcados, y las nauceas mas intensas en los niños que en los adultos. En el momento de hacer el estudio, la frecuencia de los ataques se encontraban como regla general en regreción. Por consiguiente el pronostico no parece tan desfavorable en estos casos de comienzo precóz. De 26 familias en las cuales uno u otro de los parientes presentaban una migrena severa, solamente 3 de 43 niños (edad media 7 años) habian manifestado sintomas de la misma enfermedad. Por lo tanto parecería que la presencia de migrena en alguno de los parientes, no provoca necesariamente la aparición precoz de la enfermedad en los decendientes.

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Functional Development During Infancy

by

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The public health control of healthy children of various ages in Sweden has developed to such an extent that during the three first years of life most children are subject to continuous examination with regard to their development and state of health. In some communities children between three and seven years are also included. The assessment of these children's state of health is based on the universally recognized principles for physical examination, whereby the presence of rickets is given especial consideration. To aid in the assessment of bodily development, reliable standard tables applicable to Swedish children have been compiled for the first year of life by v. SYDOW and for the other ages by BROMAN, DAHLBERG, and LICHTENSTEIN. These tables give the average weight and height for various ages and the variations thereof within the accepted normal limits.

With regard to mental and postural development, on the other hand, we are in a different situation; as yet we lack reliable normal values for Swedish children in these respects and are forced to resort to the results of foreign investigations, or to the brief information supplied in the text books. The origin of statements in the latter is often obscure, however, and we do not know how reliable they are. We possess still less knowledge of the limits of the normal variations in these respects when question arises as to whether a child's development is normal or not. It is only natural that under these circumstances the physician often feels uncertain when he is supposed, either for himself or for the child's parents, to assess the mental development of the child.

With a view to repairing this deficiency, most acutely felt

with regard to infants, the author began in 1940 an investigation of the mental and postural development in children aged one —three years. In order to check their normalcy in the first year of life, several tests for children under one year of age were included. Furthermore, as certain achievements which may be well developed at the age of three in exceptional cases may not be acquired until later, the age after three years was likewise included in the test in question. The development during the first year of life was studied in further detail at my clinic by MARIT SKATVEDT, who made a report on the primary results at a meeting of the Paediatric Section held on Feb. 2, 1947.

It is well known that there exist a large number of tests for the assessment of the mental development of the child. These are of great value in a careful analysis of the mental development and in the assessment of a number of mental partial functions. It is, however, inconceivable that the hurried clinician of a child health center, who must examine and evaluate fifteen to twenty children in the consulting hour, should be able to give each child the time demanded for carrying out all the tests considered appropriate to the child's age. Moreover, the necessary contact between examiner and child, so essential to a reliable result uninfluenced by emotional disturbance, can hardly be expected save in exceptional cases. The tests of psychic and static development designed for use in the child health control centers were intentionally made very simple so as to be practicable for the lay observer. In addition, they are few in number in order not to increase the burden of work unduly. It is necessary to leave the primary observations to the caretaker of the child, thus commonly the mother. Now it is well known that mothers are apt to exaggerate the achievements of their children and believe them capable of performing accomplishments which closer questioning reveals them unequal to. It is therefore essential that the reports of the mother be checked by the child health center nurse at her next visit to the house. Usually in the familiar surroundings of the home it is not difficult for the mother to elicit the achievement reported, if it actually was attained, in the presence of the nurse. In exceptional cases the physician of the

child health center should naturally be able to bear out the statements of the mother and the nurse.

The present investigation was made in the following manner. A number of perfectly healthy, physically well developed children registered at the child health center of the Gothenburg Children's Hospital, formerly organized and directed by the author, were selected as experimental subjects. It was made a condition, first that these children have no history that might give reason to suspect traumatic lesions at birth, nor previous encephalitis, nor any other demonstrable reason for retarded mental and postural development, and secondly that the mothers declare themselves interested and willing to cooperate. The majority of the children were without siblings. The parents belonged to varying economic and social strata from the well situated to the low income group. The children were not grouped according to sex. All of the children were under the care of their mothers in the parental homes. They were subject to continuous control at the child health center, meaning that at regular intervals they were examined by a paediatrician and their care was supervised by the child health center nurse in frequent visits to the home. This nurse gradually explained to the mothers the observations required with reference to the development of their children, and when the mothers reported a positive finding this was checked at the next house call by the nurse and eventually also by the physician at his office. The observations were entered on a table especially printed on the child's record form, with indication of the approximate age in months at which the child first showed the achievement in question.

As mentioned above, the number of different tests was necessarily very restricted. We decided on eighteen, choosing accomplishments that constitute normal everyday achievements of the child and would not necessitate unduly large demands on the judgement and powers of observation of the mother. Thus there were reports on the time when the child sat without support, when it took its first steps alone, and when it was able to run, to climb, and to walk down the stairs. There were also observations on the ages at which the child learned to grasp an object

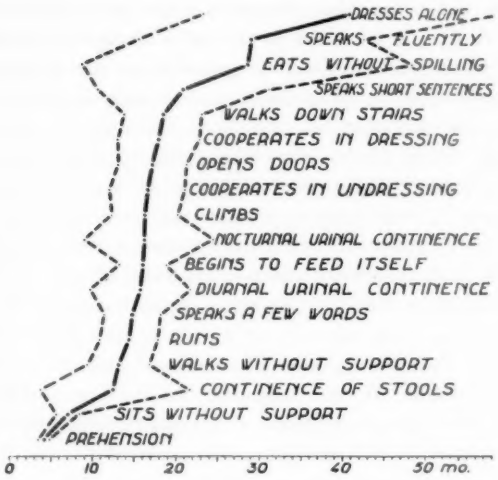
Table 1

Functional development in early childhood.

Achievements	n	Q_1	Medium μ	Q_2	Mean m	σ	$m \pm 2\sigma$	
		Number of Months						
1. Prehension	285	4	4	4	4.11	0.34	3.43	4.79
2. Sits without support	285	7	7	7	7.00	0.70	5.60	8.40
3. Continence of stools	282	10	12	15	12.40	4.33	3.74	21.06
4. Walks without support	285	12	13	14	13.04	1.87	9.30	16.78
5. Runs	270	13	14	15	14.30	1.75	10.80	17.80
6. Speaks a few words	271	14	14	15	14.71	1.69	11.33	18.09
7. Diurnal urinal continence	244	13	15	18	15.65	2.99	9.67	21.63
8. Begins to feed itself	268	15	16	17	15.94	1.42	13.10	18.78
9. Nocturnal urinal continence	215	13	16	18	16.15	4.10	7.95	24.35
10. Climbs	274	15	16	17	16.20	1.97	12.26	20.14
11. Cooperates in undressing	278	15	16	17	16.45	2.25	11.95	20.95
12. Opens doors	240	16	17	18	17.08	2.05	12.98	21.18
13. Cooperates in dressing	248	16	17	19	17.82	2.46	12.90	22.74
14. Walks down stairs	232	17	18	20	18.33	2.33	13.67	22.99
15. Speaks in short sentences	297	18	20	23	20.75	5.09	10.57	30.93
16. Eats without spilling	202	22	24	31	28.43	9.85	8.73	48.13
17. Speaks fluently	168	24	27	31	28.89	6.75	15.39	42.39
18. Dresses alone	73	36	36	48	40.58	8.75	23.08	58.08

n = number of children
Q_1 = lower quartile
Q_2 = upper quartile
σ = dispersion (with SHEPPARD's correction)

With a normal distribution of a variable (according to GAUSS's law of errors) it is assumed that $^1/_2$ % of the values fall below $-m-2\sigma$ and $^1/_2$ % over $m+2\sigma$. As the above distribution is skew there is usually *less* than $^1/_2$ % below $-m-2\sigma$ and *more* than $^1/_2$ % above $m+2\sigma$.



Functional development during infancy.

(prehension), to take part in undressing and dressing itself and finally to dress itself unassisted; to eat unassisted and finally without spilling; when it was able to open a door; and also data relevant to the development of the faculty of speech, such as when the child spoke its first words, when it was able to speak in short sentences, and when it was able to speak fluently. Finally we observed when the children were able to control stools and urine, these latter observations being divided into diurnal and nocturnal continence.

The result of this investigation and the number of subjects for each of the various achievements stated appears from the table. which consists of a statistical treatment of the material carried out in the customary manner.

The various function tests are listed according to the mean age at the attainment thereof, from the age of prehension to the age of dressing unassisted. Some of the dates naturally could not be reported according to the age in months and then the age was given in quarters. For the sake of uniformity, however, the point

of time for these data also, though less accurately definable with reference to age, is recorded in the table of age in months.

The normal variation appears best from the diagram. The earliest achievements, prehension and sitting without support, show very slight variations, but from the date of walking unassisted the variability is very large and increases further for the most advanced achievements. As is to be expected, the powers of excretory control show very wide variation and the extreme ages of the functions tested form peaks on the diagram. As appears from the results of the investigation, when a child is able to be continent as early as the age of four and one half months, there must be, first, a marked alertness on the part of the mother, who has closely observed the manifestations of the child preceding defaecation, and secondly, the child in question must belong to that special category of breast-fed children who have bowel movements only seldom, perhaps at intervals of a week or more.

It is well known that the intensity with which the mother occupies herself with the child and endeavours to call forth and train various achievements has an influence on the child's aptitude both in learning these and on the grade of its general mental development. This is perhaps especially true of the child's co-operation in dressing and undressing and its development of speech. However, such an intensive occupation with the child will advance the mental development only within certain limits, while neglect of the child, on the other hand, will appreciably retard its mental development. In exceptional cases such mental under-development owing to lack of training and contact may even lead to pseudoimbecility. In the cases included in the present study the nurses had the impression that the mothers occupied themselves with the children to a normal extent and that at all events there was in no instance any omission in this respect. I therefore believe that the course of development and the developmental variations of the groups of children investigated are in fairly good agreement with that of the average Swedish child of comparable age.

It should hardly be necessary to point out that one should

not draw unduly far-reaching conclusions with regard to retarded or advanced development in the case of deviations from the variations indicated in the diagram as normal. The reports are to be interpreted as the expression of how in all probability an entirely normal child behaves under the physiological conditions reported. The results of investigation of another and perhaps larger series might perhaps to some extent deviate from those of the present study, but these deviations would probably not be of such extent as to be of any practical importance. The present developmental diagram should accordingly serve very well as a guide in the assessment of the mental and postural functional development in early childhood.

Summary

The normal variation in the mental and postural development of the child has been studied in a number of healthy children from the child health center of the Gothenburg Children's Hospital. Statistically calculated, there is a great difference in the normal variations of different functions. Early achievements such as prehension and sitting without support show very slight variations. More advanced functions, e.g. walking capacity and excretory control, are much more individually variable. A simple diagram of functional development during infancy intended for general use in the Swedish children's welfare centers is presented.

Résumé

Etude a été faite des variations normales du développement mental et des attitudes de l'enfant chez un certain nombre d'enfants bien portants observés à la consultation de l'enfant à l'Hôpital pédiatrique de Gothembourg. L'expression statistique des faits a montré une grande différence dans les variations normales des différentes fonctions. Les premiers stades du développement psychomoteur, tels que la préhension et la station assise sans soutien ne montrent que de légères variations. Les fonctions plus avancées, telles que la faculté de marcher et le contrôle de l'excrétion varient d'une façon très individuelle. Un

diagramme simple du développement fonctionnel durant la première enfance, établi à l'intention d'un usage courant dans les dispensaires d'enfants suédois, nous est présenté.

Zusammenfassung

Bei einer Anzahl der Kinder der Mütterberatungsstelle des Gotenburgischen Kinderkrankenhauses wurden die Variationen in der normalen geistigen Entwicklung untersucht. Die Statistik zeigte grosse Schwankungen. Je einfacher die Funktionen sind, wie Greifen und Sitzen, desto kleiner sind die Schwankungen, aber um so grösser bei den komplizierteren Funktionen wie z. B. Gehversuche und selbständige Regulierung der Exkretionsvorgänge. Ein einfaches Diagramm der funktionellen Entwicklung während der Säuglingszeit zum Allgemeingebrauch in der schwedischen Kinderfürsorge ist beigefügt.

Sumario

Se ha efectuado el estudio de las variaciones normales en el desarrollo mental y postural del niño en buenas condiciones de salud, en una serie de niños del centro de Salud del hospital de Infantes de Göteborg. Los calculos estadisticos dan una gran diferencia en las variaciones normales de las distintas funciones. Las adquisiciones precoces como la prehensión, y el mantenerse sentado, muestran muy pequeñas variaciones. En cambio las funciones que son adquiridas mas tardíamente como ser la marcha y el control de los esfienteres, son mas variables individualmente. A continuación se propone un diagrama sobre el desarrollo funcional del niño para uso general de los centros de salud del niño en Suecia.

Failure at School as a School Hygiene Problem

by

J. Wickström, Åbo

During the scholastic year 1946—47, 68 157 of Finland's children attended the lower forms of our secondary schools in accordance with the system of compulsory education.[1] At the end of the scholastic year, 11 517 of them, i.e. 16.9 %, failed to obtain their removes to a higher class. The figure as such is high, but it is also high in comparison with the corresponding percentage in other countries. Thus Herlitz states that in Sweden 5.7 % were not moved up in the boys' schools, while the corresponding figure for the girls' schools was 2.9 %.

This exceptional failure on the part of the pupils in the lower forms of Finland's secondary schools cannot be regarded as a normal state of things. It is a phenomenon of so large proportions that we may be justified in speaking of it as a social shortcoming. The question requires thorough investigation, and it is my intention to deal with it from the school doctor's point of view.

In view of this situation, a social-medical-psychological investigation has been undertaken among one hundred of these second year pupils in five state schools in Åbo (Turku), of which two were girls' schools and three boys' schools, two Swedish and three Finnish. The composition of the material is shown by the following table:

[1] The secondary schools in Finland consist of an intermediate school with five forms for boys (age groups eleven—fifteen) and six for girls (age groups eleven—sixteen), and three higher forms (»gymnasium»). A large number of pupils go out into practical life after having passed through the intermediate school, while others pass on to the higher classes. This investigation does not concern these latter.

	Sex	Form	Number of Forms	Number of Pupils	Pupils Repeating Year		Examined	
					Number	%	Number	%
Svenska Flickskolan ..	Girls	I—VI	7	233	18	7.7	16	89
Sv. Klassiska Lyceum	Boys	I—V	8	209	30	14.3	26	87
Tyttölyseo	Girls	I—VI	14	470	51	10.9	20	39
Suom. Klass. Lyseo ..	Boys	I—V	6	189	32	16.9	19	59
Suom. Lyseo	Boys	I—V	13	464	76	16.4	19	25
Boys' Schools.....			27	862	138	16.0	64	46
Girls' Schools.....			21	703	69	9.8	36	52
Total Material			48	1 565	207	13.2	100	48

It will appear that the percentage of pupils repeating the year varied considerably. As is generally the case, it was higher among boys than among girls. The number of pupils repeating the year increased from the first form to the fifth form as a consequence of the steadily increasing demands of the school on the pupils.

Form	Total Number of Pupils	Pupils Repeating Year		Examined	
		Number	%	Number	%
I	374	43	11.5	17	40
II	396	51	12.9	28	55
III	289	38	13.2	17	48
IV	215	33	15.3	19	58
V	213	33	15.5	15	46
VI (Girls Only)	78	9	11.5	4	44

Constitutional Factors. — Among the causes of failure connected with constitutionally-conditioned factors, physical illness played a very insignificant part. In only one case could physical illness (nanism) be considered as the main cause of a pupil's failure. In four cases certain indications of illness may be considered as secondary causes (hypertension, congenital heart disease, congenital syphilis, mild anaemia). Delayed development (height and weight considerably below the average) was not

found in an especially high degree among the children repeating a year, but in twelve cases in which the intelligence quotient had a tendency towards low values, a short stature and low weight may have been among the causes contributing to an unsatisfactory result at school.

Symptoms of vegetative dystonicity were so marked in thirteen cases that the children's school work suffered to a remarkably high degree in consequence thereof. The importance of these symptoms in this respect is also proved by the fact that they were four times as common among children repeating a year than among the other pupils. If to these are added the cases showing disturbances of behaviour of one kind or other (undue anxiety, excessive perspiration, biting of the nails, enuresis etc.) the number of pupils with psychoneurotic symptoms rises to thirty five.

Puberty occurs for practically all pupils during the lower stage of the secondary school. Many characteristics unfavourable to school work are accentuated during this period, but as the time of puberty is difficult to define, and as its effect on the individual cannot be proved objectively enough, I have desisted from stating a puberty crisis as the main cause of a pupil's failure even in cases where this might have seemed justified.

Intellectual talents are, of course, of the greatest importance to a child's success at school. So far there are no reports concerning the average intelligence standard of the pupils of the lower secondary schools in Finland. On the basis of the investigations by RAMER, BURT, CATTELL, and HUSÉN and of my own results, it has seemed justifiable in this investigation to consider the quotients 111—120 as normal for the lower secondary school.

The average value of the intelligence quotient for the total number of pupils repeating a year was 107.5. The average quotients for the various schools were as follows:

Svenska Flickskolan	(girls)	96.7
Sv. Klass. Lyceum	(boys)	108.1
Tyttölyseo	(girls)	108.3
Suom. Klass. Lyseo	(boys)	108.5
Suom. Lyseo	(boys)	114.1

For the boys the average quotient was 110.0, for the girls 103.1, and the median values were 109 and 99, respectively. The distribution of the intelligence quotients of the pupils repeating a year may be seen from the following table:

	76—80	81—85	86—90	91—95	96—100	101—105	106—110	111—115	116—120	121—125	126—130	131—135	136—140	Total
Svenska Flickskolan	1	—	3	4	5	—	1	—	1	1	—	—	—	16
Tyttölyseo	—	—	1	2	4	1	4	3	1	2	1	—	1	20
Sv. Klass. Lyceum	—	3	2	2	1	1	7	1	2	5	—	1	1	26
Suom. Klass. Lyseo	—	—	1	—	3	6	2	4	1	—	—	—	2	19
Suom. Lyseo	—	—	—	—	—	2	7	4	1	1	3	1	—	19
Girls' Schools	1	—	4	6	9	1	5	3	2	3	1	—	1	36
Boys' Schools	—	3	3	2	4	9	16	9	4	6	3	2	3	64
Total	1	3	7	8	13	10	21	12	6	9	4	2	4	100

Of one hundred children repeating a year, thirty two had an IQ below 100. It may be considered that they lacked the intellectual qualifications for secondary education. For the thirty one pupils whose IQ's lay between 101 and 110, and who thus were normally talented pupils below the average level of the lower secondary school, mediocre talents were a handicap which in many cases could be compensated by ambition and other favourable traits of character. Within the intelligence group which is here considered normal for the lower secondary school, there were eighteen pupils repeating a year, while nineteen were talented pupils with a quotient between 121 and 140.

The intelligence quotient was lowest among the pupils repeating the first form and in each form was higher than in the previous one:

Form I,	number	repeating	pupils	examined	17,	average	quotient	99.6
II,	»	»	»	»	28	»	»	104.1
III,	»	»	»	»	17	»	»	109.0
IV,	»	»	»	»	19	»	»	112.3
V,	»	»	»	»	15	»	»	112.7
VI [1],	»	»	»	»	4	»	»	116.5

[1] Girls only.

This circumstance, together with the percentage of pupils repeating, which is higher in each successive form, show that the qualifications of a pupil for lower secondary education have to be judged with the demands of the top form in view.

In this material those who were too young for their forms were evenly distributed in the different forms (they varied from 12.7 % to 14.3 %). The proportion of these among the pupils repeating was the same as among the total number of pupils. Their standard of intelligence was high compared with that of repeating pupils of normal age or with that of the over-age pupils in the form:

2 years too young for form,	3 pupils,	average IQ	133.7	119.0
1 year » » » »	12 »	»	115.4	
Normal age	33 »	»	110.5	
1 year too old for form	37 »	»	103.1	102.3
2 years » » » »	10 »	»	104.4	
3 » » » » »	5 »	»	92.2	

Their intelligence age apparently corresponded with the intelligence age of the form, and judging from these figures they failed for reasons not purely intellectual.

Environment factors may be of as great importance to school work as the constitution. To a certain extent especially, good home conditions may help an intellectually poorly-equipped pupil in achieving satisfactory results. On the other hand, it is quite obvious that bad environmental conditions may cause the failure of pupils with adequate constitutional qualifications for successful school work.

In this material split or disharmonious families amounted to no less than twenty nine. In twelve cases the father had died or left the home and in five cases the mother. In at least nine cases alcohol played its part in causing discord. The conditions in which the child was thereby placed were satisfactory in sixteen cases and unsatisfactory in thirteen.

Even if the family had no distinctly negative influence on the child, it was not always able to influence its school work favourably. As the result of much too large classes — three fifths of them had more than thirty pupils — the teachers lacked the time

to pay all pupils enough attention. The homes had therefore to give their support. In homes where the parents themselves have benefited from secondary education an intellectual atmosphere is created which stimulates the development of the child. Such was the case with only one third of these second year pupils. The majority came from homes where such conditions did not exist. The capacity for giving the children a character-moulding education was also often lacking in these homes.

Home conditions had deteriorated in consequence of poverty in fifteen cases, there were overcrowded housing conditions with at least three persons per room in sixteen cases, and there were neglect and carelessness in twelve cases. Thus the conditions for preparing lessons at home had been unsatisfactory for fifteen pupils.

As a factor in environment the school, too, plays an important part. Large classes prevent the teachers from taking special care of the weaker pupils. In this case failure often leads to a marked tension between home and school, and the chances of achieving a satisfactory result are then small for the pupil.

Indifference, so very common, is often conditioned by the fact that the teachers are not able to devote enough time to the pupils to keep their interest in school work alive even when difficulties at school or powerful rival interests appear. In this material there were only a few pupils who could be considered really indolent in the sense that they preferred being inactive. The indifference of the others meant that school work could not capture their interest, but most of them had something to keep them occupied. They did their lessons as little as possible in order to have more time for their hobbies. This applied especially to the most talented pupils with an intelligence quotient above 120. Their leisure time interests were usually numerous and keen. For fifteen of the nineteen pupils in this group indifference had been the main cause of their failure. In the large classes the teacher has not time to get to know his pupils; thus it happened once that the form master stated stupidity to be the cause of a certain pupil's failure although the latter's IQ proved to be 140.

The Main Cause of the Failure of Pupils Repeating a Year. — Obviously it is difficult to measure the importance of the causes

mentioned in relation to one another in every case. When, however, one factor could be considered to have contributed to the failure of the pupil to a larger extent than others, every case was examined with regard to the main cause and secondary circumstances. This examination gave the following results.

	Physical Illness or Weakness		Psychical or Psychosomatic Disturbance		Low Intelligence		Environment		Indifference		Rival Interests	Too Young	Poor School Attendance	Total
	++	+	++	+	++	+	++	+	++	+	+	++	+	
Sv. Flickskolan .	1	2	—	4	12	2	1	9	2	8	2	—	7	16
Sv. Klass. Lyc. .	—	4	1	4	8	8	3	3	12	6	7	2	7	26
Tyttölyseo	—	1	7	2	7	5	—	5	5	3	2	1	4	20
S. Klass. Lys. ..	—	7	1	5	6	6	1	1	11	5	8	—	5	19
Suom. Lys.....	—	2	3	4	2	8	—	9	14	2	5	—	3	19
Total ++	1		12		35		5		44			3		100
+		16		19		29		27		24	24		26	165
Boys	—	13	5	13	16	22	4	13	37	13	20	2	15	64
Girls	1	3	7	6	19	7	1	14	7	11	4	1	11	36

++ main cause, + secondary cause.

These figures show that physical illness was very seldom the main cause of a pupil's failure. On the other hand, it seemed advisable to take conditions of physical weakness (delayed development, malnutrition, slight anaemia etc.) into account as secondary causes in cases in which several factors co-operated.

Psychical disturbances of a more serious nature were also rare. In one case a hysterical disposition and in another marked schizothyme characteristics had had an obstructive effect on the school work. In one case extreme phlegm was obviously the cause of the unsatisfactory result at school. Symptoms of vegetative dystonicity were of decisive importance to the school work in nine cases, partly because they brought on excessive lassitude which impeded the work of the pupil and partly because of the anxiety which kept the pupil from displaying his knowledge to full advantage.

The chief cause of failure was, however, to be found in inadequate intellectual talents. In every third case this was the main reason for failure. If pupils with an IQ between 101 and 110 were placed in this category — which seems justifiable in view of the present demands of the lower secondary school, although on the basis of this limited investigation I am not inclined to recommend such a rigorous selection — it would comprise up to about two thirds of all pupils repeating a year.

Factors of environment spoiled the results of the scholastic year for five pupils and contributed less directly to twenty seven pupils' not having obtained their remove.

Under the heading »indifference» those cases have been collected which give a school doctor very small chances for judgement, and where the investigation of the problems falls within the scope of the teacher or psychologist. In these cases insufficient interest in school work, incapacity for concentrating on the task, discomfort at school, and a desire for practical work etc. are responsible for forty four pupils' having remained a second year in the same form. In many cases indifference to school work was combined with rival interests outside the school, but these are difficult to judge and have here been labelled only secondary causes. Among these cases there were many pupils whose symptoms were aggravated by a puberty crisis.

Three repeating pupils were two years too young; in their cases this must be considered the main cause of their unsatisfactory work.

Intermittent school attendance was regarded as only a secondary cause, even when the pupil had changed school six years in succession or been to seven different schools in the course of ten years.

There was a marked difference between the causes of failure among boys and among girls. For boys indifference was the dominating factor (about one half of the cases); in second place came insufficient intelligence (about one fourth of the cases). Among the girls stupidity dominated (a good one half of the cases), while indifference played a less prominent part (about

one fifth of the cases). Nervous symptoms were more common among girls than among boys.

The causes of failure were subject to change at different stages of the lower secondary school, as may be seen from the following table giving only the main causes:

	Physical Illness	Psychical or Psychosomatic Disturbance	Low Intelligence	%	Environment	Indifference	%	Too Young	Total
Form I	—	2	9	(53)	1	4	(24)	1	17
II	—	3	14	(50)	1	10	(36)	—	28
III	1	2	4	(24)	2	7	(41)	1	17
IV	—	3	5	(26)	—	10	(53)	1	19
V	—	1	3	(20)	1	10	(67)	—	15
VI[1]	—	1	—		—	3	(75)	—	4
Total	1	12	35		5	44		3	100

[1] Girls only.

While low intelligence was the cause of failure in half of the cases in the two lowest forms, in the higher forms it was confined to one fourth—one fifth of the cases. Indifference to school work increased successively from one fourth in the lowest form to three fourths in the top form.

Pupils Repeating a Year as a School Hygiene Problem. — At present there is an obvious disproportion between the demands of the lower secondary school and the capacity of the pupils to satisfy these demands; this is proved unmistakably by the abnormally high percentage of pupils repeating a year. A more rigorous sorting out would be extremely desirable, partly in order to keep the classes within reasonable limits, partly in order to eliminate the pupils who have not the qualifications for secondary education but who obstruct the teaching in general. Investigations by LEHTOVAARA have proved that the marks given by the elementary schools present a better picture of the chances of the pupils than an entrance examination. Pupils with low marks

in the elementary school should be intelligence-tested before admission to secondary schools.

In connection with this admission, which should take place at the end of the spring term, the new pupils should undergo medical examination. Physical conditions of illness or debility may, if they are noticed then, be improved in many cases through suitable treatment during the summer. Psychosomatic disturbances can be investigated and the pupil's problems put before the teacher when school work begins in the autumn.

In cases where the pupil presents problems of any kind, the school nurse should visit the home at this early stage in order to investigate the existence of injurious environmental factors which might be eliminated.

As the majority of pupils who fail seem to be without adequate support at home, it seems to be necessary to establish contact between school and home at an early stage in order to discuss the problems which face an unsuccessful pupil. And as there is reason for adopting the point of view that every pupil repeating a year is a school hygiene problem, it would be desirable, if failure seems to threaten, to summon the form master, the school doctor, the school nurse, and the pupil's parents to discuss together the difficulties which have been noticed. This should happen early in the spring term. In this kind of work the school doctor has great qualifications for making a contribution; he should be able to throw light on the pupil's problems and help teachers and parents to take suitable steps.

Summary

The author has undertaken a social-medical-psychological investigation among one hundred pupils in the lower secondary school (intermediate school) who failed to obtain their removal to a higher form. As causes of their failure physical illness or physical weakness played a subordinate part (one case). Vegetative disturbances and psychoneurotic disturbances of behaviour played a decisive part in twelve cases. Insufficient intelligence (IQ below 100) was established in thirty five cases. Failure was caused by unsatisfactory environmental conditions in

five cases and by insufficient development (two years too young for the form) in three cases. In the remaining forty four cases indolence was the dominating factor.

The author considers failure at school to be a school hygiene problem, the solution of which requires the cooperation of the school doctor.

Résumé

L'auteur a entrepris une investigation socio-médico-psychologique parmi 100 élèves de classes secondaires inférieures (classes intermédiaires) qui n'ont pas obtenu leur admission en classe supérieure. En tant que cause de leur échec, la maladie ou la défaillance physique ne joue qu'un rôle secondaire (1 cas). Des troubles végétatifs ou neuropsychiques du comportement jouent un rôle décisif dans 12 cas. On reconnut une intelligence insuffisante (coefficient en dessous de 100) dans 35 cas. Les causes de l'échec sont de mauvaises conditions dues à l'entourage, dans 5 cas et un développement insuffisant (2 ans trop jeune pour la classe), dans trois cas. En 44 cas l'indolence représente le facteur dominant.

L'auteur considère que la non-réussite en classe est un problème scolaire d'ordre hygiénique, dont la solution requiert la coopération du médecin scolaire.

Zusammenfassung

In einer Mittelschule wurden 100 Schüler, die nicht das Klassenziel erreicht hatten, sozialmedizinisch und psychologisch untersucht. Krankheit oder physische Schwäche spielten eine Rolle nur in einem Falle. Die weiteren Untersuchungen ergaben in 12 Fällen vegetative und psychoneurotische Störungen, in 35 Fällen ungenügende Intelligenz (IQ unter 100), 5 Fälle wegen schlechter sozialer Verhältnisse. 3 Fälle erwiesen sich als nicht schulreif (2 Jahre jünger als die übrigen). Eine dominierende Rolle spielte in 44 Fällen Faulheit.

Der Verfasser nimmt das Nicht-Vorwärtskommen in der Schule als ein schulhygienisches Problem an und schlägt eine engere Zusammenarbeit mit dem Schularzt vor.

Sumario

El autor ha realizado un estudio medico-social y psicológico de 100 alumnos de la escuela secundaria, que no han sido promovidos a estudios superiores. Como causa de esta deficiencia psíquica o debilidad psíquica encuentra que los trastornos vegetativos juega un papel muy poco importante, un solo caso, mientras que las alteraciones psiconeuróticas de la conducta jugaron el rol decisivo en 12 casos. Pudo constatarse una deficiencia de la inteligencia en 35 casos (I.Q. por debajo de 100). Esta insuficiencia fué causada por condiciones no satisfactorias del medio ambiente en 5 casos, y por un desarrollo insuficiente (dos años menos al correspondiente a la edad) en tres casos. En los 44 casos restantes la indolencia constituyo el factor dominante. El autor considera que esto constituye un problema de higienen escolar, cuya resolución requiere la cooperación del medico escolar.

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FROM THE SACHS CHILDREN'S HOSPITAL, STOCKHOLM.
CHIEF: J. HENNING MAGNUSSON, M.D.

Hemiscleroderma Alternans

by

ROLF ZETTERSTRÖM

Scleroderma appears mainly to affect the mesenchymal tissue, but since the pathological lesions can appear in a variety of forms and are also in many cases combined with disturbances in different internal organs, the symptomatic picture can vary considerably. Despite many attempts to explain its genesis, the aetiology of this disease is not yet elucidated.

The skin process is characterized by indurative and, later, degenerative lesions, atrophy, and sclerosis with resulting discolouration, pigmentation, or vitiligo. Three different forms can be distinguished (HÄMÄLÄINEN and SÖDERLUND): 1) progressive diffuse scleroderma, usually localized to the face, neck and trunk; 2) sclerodactylitis affecting the distal parts of the extremities; and 3) scleroderma »en plaques», in which distinctly local plaques appear which sometimes become confluent later. In between these three types there are, however, many intermediate forms. Of these, so-called scleroderma »en bandes» is of particular interest, since it appears in band-shaped zones with an area corresponding to the metameres. There is nearly always fibrosis and atrophy of the underlying muscles in these areas which may rapidly lead to severe contractions. ELLERMAN has described a case of a six year old girl in whom muscular fibrosis developed before the onset of the skin lesions. Pronounced atrophy of the bones may also occur.

The disease is usually circumscribed at the onset, with one or two oedematous infiltrations with a slight reddish or bluish discolouration and an indistinct transition to the healthy tissue. There is generally a paler and tender area in the center. Accord-

ing to PAUTRIER and WORINGER, this is due to a vasodilatation in the peripheral parts resulting in angiospasm or sclerosis of the narrow blood vessels. Morbid changes can be observed in the capillaries and the small blood vessels, the papillae of the skin, the muscles, and the internal organs. Plethysmography nevertheless registers normal results (MARINESCO AND ASSOCIATES).

There are many indications that the condition can be caused by disturbances in the endocrine system. A concomitant subcutaneous deposit of calcium may occur with the other skin lesions (THOMAS, MYHRMAN and MALMSTRÖM, and others), sometimes so pronounced that calcinosis universalis arises (GRAHAM). PAUTRIER and ZORN (quoted by LERICHE) found hypocalcaemia in 70 % of collected cases of scleroderma. LERICHE and JUNG were therefore of the opinion that the disease is caused by a parathyroid hyperfunction, particularly since they considered that they were able experimentally to induce a scleroderma-like picture through overdoses of parathyroid hormone. Parathyroidectomy should therefore be a suitable form of therapy. MARINESCO later found normal serum calcium in a number of cases in a large series.

The disease can be congenital and is then most frequently combined with symptoms of endocrine insufficiency. The most common type is progeria, i.e. hypophyseal dwarfism with signs of Simmond's disease and concomitant diffuse scleroderma. According to ZEDER, who assembled ten cases of this syndrome from the literature and reported one of his own cases, scleroderma is a symptom of a disturbance in the calcium metabolism. This disturbance of the mineral metabolism would in turn be conditioned by a hyperfunction of the parathyroid as a result of injuries to the anterior lobe of the hypophysis cerebri. Hypophyseal damage with congenital scleroderma need not, however, always give rise to typical progeria; MÜLLER-HESS has described a case in which there was no dwarfism. His patient, on the other hand, suffered from bilateral cataract. This symptom appears to be fairly common in various descriptions of cases of congenital scleroderma (MONIER, VINARD and BARBOT, etc.).

Among other symptoms, mention may be made of serositis,

arthropathy, and osteosclerosis. BARLOW's report of the post-mortem finding of a bilateral adrenal tumour in a fifty one year old patient with scleroderma shows that the disease also appears to be caused by functional disturbances in other endocrine organs. Typical skin lesions have also been observed in Basedow's disease.

The segmental arrangement corresponding to the metameres found in scleroderma »en bandes» (VOHWINKEL, WAGNER, and others) distinctly indicates a neurogenic influence. The sympathetic nervous system is assumed to be the neurogenic factor the dysfunction of which gives rise to an increased tonicity in the small blood vessels, secondarily causing trophic disturbances. Disorders in the autonomic nervous system might also give rise to endocrine abnormalities. In progeria, the autonomic nervous system is in a state of increased stimulation which, according to ZEDER, is evident in functional tests. Nevertheless, a disturbance in the troponeurotic centers taking effect through the sensory nervous system can never be excluded.

Several theories exist regarding the localization of the site of attack on the neurogenic apparatus. BRUNS considers the cause to be lesions in the medulla oblongata with its autonomic centers. The vasomotor supply is also closely correlated with the spinal centers and the spinal ganglia and SEQUEIRA therefore believes the diseases to depend on changes in the spinal ganglia. Herpes zoster can be considered a parallel disorder. This disease, with a typical segmental distribution, usually arises as a sequela of inflammatory lesions in the ganglia of the spinal cord or of the cerebral nerves. According to MARINESCO, the vasomotor and trophic disturbances emanating from the autonomic nervous system are of infectious-toxic origin. This aetiological hypothesis is supported by the occurrence during the course of the disease of symptoms reminiscent of a rheumatic infection.

ORRICO and GAREISO have each reported one case of scleroderma with a positive Wassermann reaction. The onset of the disease may resemble that in an acute infection; in one case (SCHÄFER) it was characterized by pronounced lethargy and a lack of facial expression, thus presenting the picture of acute encephalitis. There are also certain possibilities that the congenital

syndrome in scleroderma may be a sequela of intrauterine infections.

The course may either be rapid, with a fatal outcome in a short time, or extend over several decades. Most frequently, however, the onset of the disease is so slow and insidious that it is difficult to establish the exact time. The patient frequently states trauma to be the cause (LÖFSTRÖM).

Even when the onset has been acute, the disease may later remain stationary or even show distinct regression, in which case the skin appears to regain its capacity for normal nutrition and its elasticity is restored, while the condition of the patient is considerably improved. The contractions have always remained, however.

The disease can occur at any age, with a possible predominance in the years immediately following puberty. There appears to be a slightly higher incidence among women.

Different therapeutical methods have led to no convincing results. In addition to symptomatic therapy, parathyroidectomy and various interventions on the sympathetic nervous system (LERICHE, HÄMÄLÄINEN) have been performed.

The facial hemiatrophy pointed out by several writers (ALVAREZ, GAREISO, HUNT, VOHWINKEL, and others) would be a scleroderma »en bandes» localized within the trigeminus region. The disturbance has usually been confined to one side of the face and considered to have its origin in the gasserian ganglia. When the affection is combined with sclerodermic lesions on the trunk and the extremities, multiple ganglionic damage would exist by analogy. Nevertheless, cases have been described in which the skin symptoms with accompanying atrophy of the bones and muscles were strictly localized to one side of the face and the opposite of the remainder of the body (BARCAGLIA, HUNT, MARINESCO). The cause of this alternating type is presumably an injury to the central nervous system with its site in the region of the pons varolii, unless an extremely strange localization of the ganglia is present.

A report is given in the following of a case observed by the present writer at the Sachs Children's Hospital, Stockholm.

The patient, a girl aged four years, was admitted to the hospital on Oct. 15, 1947 (826/47). There was nothing of interest in her heredity. She was the only child of healthy parents: birth weight 3 100 g, parturition normal. She was given breast milk only for the first six months. There were slight dyspeptic disturbances in connection with weaning carried out according to instructions from the Child Welfare Center and during subsequent years there were frequent but always slight digestive disturbances. In December 1945, she had pertussis with a mild course. Otherwise she was healthy on the whole until the onset of the disease in question. She manifested slightly neurolabile traits. Her physical and mental development were normal.

In September 1946, at the age of three, she became acutely ill with signs of a hyperpyretic catarrhal infection. After a few days a soft, subcutaneous, pale, tender swelling developed on the left hand and foot joints. The temperature returned to normal after four days, but the swelling persisted and became indurated and firmer at the same time that blue discolouration appeared on the skin. She was treated at the Outpatient Department of the hospital, where acute polyarthritis was first suspected. MSR 40 mm/hr.

The skin changes spread over the left hand and forearm and the left lower leg. The joints were altogether normal.

The patient was admitted to the hospital one month after the onset of the illness. Her psychic condition was then abnormal; she was lethargic, uninterested in her surroundings, depressed, reserved, and seldom spoke. Her facial expression was blank. She evidently shrank from light, although there was no conjunctivitis, and she perspired freely. Apart from the skin lesions the somatic condition was completely ordinary. During the month she spent in the hospital the psychic disturbances regressed entirely but the skin lesions progressed somewhat. Although neither acrocyanosis nor hypotonicity was present, the disease was considered to be a form of acrodynia because of the concomitant skin lesions and psychic disturbances. Lumbar puncture was not performed.

At the end of December in the same year, three months after the onset, the skin lesions showed a tendency to exacerbation; the skin on the left arm and leg became rigid and hard and the earlier bluish colour changed to a yellow-brown tinge. Some stiffness was also present in the muscles and movement became more difficult. Nevertheless, with some active effort the motility of all the joints was still relatively good.

She was admitted to the dermatological department in January 1947. She was then afebrile, lively, contented, and generally unaffected. There

were no signs of infection and no abnormalities of the internal organs. The skin of the left hand and on the dorsal aspect of the arm, which showed a diffuse transition to normal skin on the shoulder and on the flexor aspect, was pale yellow, somewhat atrophic, and firmly adherent to the infiltrated underlying tissue and could not be lifted in folds. Similar lesions on the left leg, most pronounced around the ankle and lower leg, extended to the upper part of the thigh, where they terminated on the anterior aspect with a band-shaped discolouration extending obliquely downwards and medially. The right ankle and foot showed similar but less pronounced lesions. There was a similar limited skin infiltration on the left side of the abdomen. On the left shoulder and the left side of the back there were some long pale areas of skin in which a distinct depigmentation could be seen in small patches.

A blood count showed slight to moderate eosinophilia, 4—8 % eosinophils, but otherwise nothing abnormal. Heller positive in some tests. Fairly plentiful WBC in the urinary sediment; probably an infection of the urinary tract. MSR 70 mm/hr. Mantoux (1 mg) negative. W.R. in the blood negative. Serum calcium, phosphorus, and phosphatase within normal limits. X-ray of the left arm and leg revealed no abnormalities. Biopsy: no definite changes in the epidermis. No pronounced atrophy. The corium appeared thicker than normal, with dense, coarse collagen fibrils. There were fat lobules enclosed in the fibrils in the deep part of the connective tissue, indicating deep-seated fibrosis. Slight inflammatory infiltration in the corium, chiefly with round cells and localized to the small vessels, was noted. The walls of the latter were often thickened, with formation of new connective tissue in the adventitia. The picture was not particularly characteristic, but the thickening and density of the corium, the inflammatory infiltration, and the blood vessel changes could have indicated scleroderma. Similar clinical pictures also occur in dermatomyositis (RINGERTZ).

Despite intensive penicillin therapy and subsequent administration of thyroid, the disease progressed. The stiffness in the left arm and leg increased with the spreading of the skin sclerosis. Contractions developed in all the joints of the extremities involved. The patient was discharged after two months' hospitalization owing to the rapid progression of the disease during that time and the extremely poor prognosis.

In the spring of 1947 there was additional sclerosis on the right side of the face and the left side of the neck and the nape. Alopecia over the superior part of the frontal and sincipital regions. At the end of September there were trophic ulcers on the left knee and the right superior area of the frontal bone.

The patient was admitted to our hospital in the middle of October with an acute infection of the throat and urinary tract. This regressed rapidly after a few days' chemotherapy. In the affected areas the skin

was generally atrophic. In the parts most mildly involved it was shiny and smooth. In the more severely affected areas the skin was extremely thin and covered in patches with numerous, partly secondarily-infected erosions, either watery or crusted. They were indurated, adherent to the underlying tissue, scarred and striated, and partly changed to plaques. Some patches had a yellowish-brown pigment, while others were pale as in vitiligo.

On the left knee there was a sharply defined, fairly deep secondarily-infected ulceration, about two centimeters in diameter, with plentiful granulation tissue. There was a similar ulceration about 5 cm × 7 cm in the right frontal region. There was tenderness in the eroded skin areas and itching in the crusted ones. At the same time there was pronounced atrophy of the subcutaneous tissue and the muscles of the right half of the face, the left arm, and the left leg. With the exception of the distal finger joints, there was practically total contraction of all the joints of the left arm and leg. There was traction of the mouth to the right. The right eye-opening was slightly smaller than the left. The patient sat with her body inclined to the right; there was pronounced scoliosis, convex to the right. An area in the face sensorily innervated by the first and third branches of the right trigeminus nerve was affected. That part of the face supplied by the second branch of this nerve was practically unaffected. The skin was sclerotically changed in the area innervated by the left cervical plexus. The more severe lesions on the trunk and the extremities were localized to the left half of the body, a particularly distinct medial borderline appearing on the abdomen and chest. There were very slight lesions in the right hemisphere of the body around the mamilla, on the dorsal aspect of the hand and arm, and on the anterior aspect of the leg. With the exception of the lateral aspect, the anterior part of the right foot showed a fairly pronounced sclerotic area. There was no reduction of motility in any of the joints in the right hemisphere of the body.

When the acute infections had regressed, there were no abnormalities in the mucosa or the internal organs. There was a slight elevation of the blood pressure, i.e. 120/80 on repeated readings, and slight tachycardia, approximately 100—120/min. The patient's mental condition was on the whole pleasant; she was cheerful and friendly and had a positive attitude to her surroundings. Her mental development was normal for her age. Her mobility was surprisingly good. In addition to the contractions, there was atrophy of the skeletal muscles and slight dextrolateral atrophy of the tongue. There were no demonstrable neurological disturbances. Cerebrospinal fluid normal. Electromyelography: M. biceps sin. No grounds for assuming damage to the peripheral motor neuron (KUGELBERG). Investigation of the autonomic nervous system gave negative results. No dermographia. It is possible that the slight

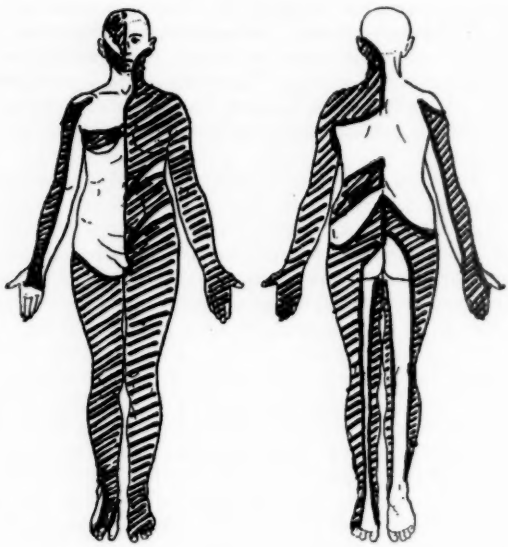

Fig. 1. The shaded areas mark the affected parts of the skin. In the left hemisphere of the body the extent corresponds mainly to the segments C 2—C 5, D 1—D 5, D 8—D 9, D 12, L 1—L 4, and partly L 5 and S 1—S 2. In the right, it corresponds to the first and third trigeminus branches, C 5—C 8, D 4, and L 2—L 5. With the exception of the face, the scleroderma is considerably more pronounced on the left than on the right side. In the latter, in which the process involves the trunk only slightly, the skin of the extremities is merely thin, slightly atrophic, and somewhat firmer than normal. This is seen distinctly in the photograph.

elevation of the blood pressure and the constant tachycardia could be interpreted as a result of the irritation of the sympathetic nervous system.

The microsedimentation reaction was elevated, being 50—70 mm/hr. With the exception of 8 % eosinophils the blood picture was normal. Serum calcium 10.2 mg%, inorganic phosphorus 4.2 mg%. After regression of the infection of the urinary tract the findings in the urine were normal. There was no creatinuria.

X-ray examination showed the following: lungs and heart N.A.D. Possible slight atrophy on the right side in the facial skeleton. Right arm and leg N.A.D. General decalcification of the bones of the left

arm and leg, particularly the foot, in which they were almost as transparent as glass.

ECG: sinus tachycardia, otherwise N.A.D.

Dicumarin therapy was started and the skin appeared to become somewhat softer. The patient, who had earlier had difficulty in eating owing to the tautness round her mouth, found it considerably easier to chew her food. The treatment was continued for five weeks, after which the patient was sent home. The ulcerations were then entirely healed and the skin was dry on the whole body.

The patient was examined in the middle of January 1948. Her condition was then on the whole unchanged.

On examination in October 1948 the skin lesions showed a pronounced tendency to regression. The skin on the trunk was practically normal. There was also an improvement in the face and the extremities, but the contractions were unchanged.

Summary of the Case History. The child became ill at the age of three after a catarrhal infection of short duration. The clinical picture resembled encephalitis, with mainly psychic symptoms and a concomitant induration of the skin of the left hand and foot joints. The psychic symptoms regressed after about two months. Within a year there were progressive scleroderma-like cutaneous lesions of the scleroderma »en bandes» type. These were found chiefly on the right half of the face and the left half of the body; on the right half of the body the lesions were confined to the lower extremities. In the affected areas the subcutaneous tissue and the musculature were firm, hard, and atrophic and the bony skeleton decalcified. Pronounced contractions in the left arm and leg. During subsequent years there was slow regression of the cutaneous lesions.

Discussion

The case reported is thus a form of hemiscleroderma alternans with a distinctly segmental distribution and concurrent atrophy of the underlying tissue.

The course of the disease appears to indicate an infectious genesis, and the transient psychic and mainly lethargic symptoms occurring after a catarrhal infection can be interpreted as encephalitis. The circumstance that the localization of the more severe sclerodermic lesions was mainly alternating hemilateral seems to point to a central lesion with its site in the pons varólii area. That no demonstrable endocrine disturbances were present may have been due to the localization of the injury. If it had been higher up, in the mesencephalon, endocrine disorders as well as the trophic autonomic ones could have occurred. This appears to be the case when the disease is congenital and there is pluriglandular insufficiency.

At the start the disease showed some similarity to acrodynia, despite the absence of one or two typical symptoms. The aetiology of acrodynia is considered by many writers to be infectious, the disease then being caused by a neurotropic virus with a particular affinity to the autonomic nervous system. By analogy the type

of scleroderma described could arise through the effect of a similar agent.

No study of the incidence of hemilateral scleroderma has been made, but on the basis of the literature available it appears that the disease occurs mainly in sub-tropical regions and particularly in Brazil. Various forms of encephalitis and acrodynia also show a high incidence in certain geographical areas.

Summary

A report is given of a case of hemiscleroderma alternans with atrophy of the skeleton and musculature in a four year old girl. The disease had its onset one year earlier in connection with symptoms resembling encephalitis.

In view of the course of the disease and the symptomatology, an infectious aetiology appears probable. An injury localized to the pons varolii area could have caused the autonomic-trophic disturbances with atrophy and sclerosis.

Résumé

Hemiscleroderma alternans

On rapporte un cas d'hemiscleroderma alternant avec atrophie du squelette et de la musculature, chez une fillette de 4 ans. Les premières manifestations de cette maladie remontent à un an, et s'accompagnèrent de symptômes ressemblant à ceux de l'encéphalite.

Vu l'évolution de la maladie et sa symptomatologie, une étiologie infectieuse paraît probable. Une lésion localisée dans la région du pont de Varole pourrait causer les troubles trophiques autonomes avec atrophie et sclérose.

Zusammenfassung

Hemiscleroderma alternans

Es wird über einen Fall von Hemiscleroderma alternans mit Atrophie des Skelettes und der Muskulatur bei einem vierjährigen Mädchen berichtet. Die Krankheit setzte ein Jahr vorher mit Symptomen ein, die einer Gehirnentzündung ähnlich waren.

In Anbetracht des Verlaufes der Krankheit und der Symptomatologie scheint eine ätiologische Infektion aller Wahrscheinlichkeit nach vorzuliegen. Eine Verletzung, die sich auf das Gebiet der Varolsbrücke lokalisierte, könnte die autonomisch-trophischen Störungen mit Atrophie und Sklerose hervorrufen.

Sumario

Hemiesclerodermia alternante

Se describe un caso de hemiesclerodermia alternante con atrofia del esqueleto y de la musculatura en una niña de 4 años. La enfermedad habia debutado un año antes en conexión con sintomas al parecer de encefalitis.

Considerando el curso de la enfermedad y la sintomatologia, parecería probable una etiología infecciosa. Una lesión localizada del area del puente de Varolio podria ser la causa de los trastornos troficos-autonomos, con atrofia y esclerosis.

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FROM THE MEDICAL DEPARTMENT OF THE CHILDREN'S HOSPITAL, GOTHENBURG.

Electrocardiography in Prolonged Asphyxia Neonatorum

by

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In intrauterine asphyxia the signs of most practical value are cardial. Asphyxia expresses itself clinically by changes in the frequency of the heart sounds, especially in the form of bradycardia. Pathogenetically, anoxia and hypoxaemia are of dominant importance in intrauterine asphyxia.

In asphyxia of the newborn the symptomatology is richer. This is due among other things to the fact that — unlike the asphyctic foetus in utero — direct observation of the victim is now possible. The predominant and most valuable pathognomic in asphyxia neonatorum is insufficient respiration (during intrauterine life pulmonary respiration plays, of course, no part in the oxygen supply). Independent of the pathogenesis of asphyxia neonatorum — which is often more complicated and more difficult to judge than that of uterine asphyxia — the child's life depends on the initiation of respiration. Insufficient respiration leads to hypoxaemia, which in turn impairs the sensibility of the respiratory centres. An anoxaemic cerebral derangement is thus always present in asphyxia neonatorum. But anoxia also impairs other essential organs and functions, among them the heart and the circulation. Bradycardia, arrhythmia, faint heart sounds, and pallor are some of the most common signs indicative of cardiovascular involvement. As a rule, mild or moderate asphyxia neonatorum has a good prognosis, and a relatively quick recovery with a comparatively prompt abatement of the cerebral and cardiovascular dysfunctions may be expected. In very serious cases the markedly insufficient respiration — often manifest in the

form of total or almost total apnoea — soon leads to death, i.e. to a sudden, irreversible anoxic damage of, among other organs, the brain and the heart. There is, however, an intermediate degree of prolonged asphyxia neonatorum in which the infant hovers for hours or days between life and death, and in which persistent or recurrent insufficient respiration with its subsequent effect on the brain and the heart or circulation is present. In view of the decisive importance of the heart and circulation in the transport of oxygen and thus the aeration of the brain and the reciprocity between the respiration and circulation, the functionability of the heart under these abnormal conditions undoubtedly plays an important role.

With this in mind I thought it might be interesting to make electrocardiographic examinations of newborn infants with persistent asphyxia neonatorum. The observations I have hitherto made will now be briefly reported.

Case 1. (1312/47.) Boy b. July 3, 1947. Wt. 3 510 g. Died July 5, barely two days old. Full-term delivery. Mother Para I. Prolonged partus; foetal sounds shortly before partus slow. Infant appeared asphyctic at birth. Abundant mucus sucked up from throat. At first the child recovered well after asphyxia but afterwards gradually became cyanotic and stiff. Later his general condition again seemed to be good; his colour was normal and respiration regular. On the morning of July 5 a severe attack of cyanosis occurred and the baby was therefore transferred to the Children's Hospital. Condition on admittance: generalized pallor and slight cyanosis. Respiration shallow, accelerated, about 76 per min. Heart beat about 70 per min., now and then irregular rhythm and gallop rhythm. General hypertonia. No convulsions. Towards evening cyanosis became more profound and respiration began to fail. The infant died at 10 p.m. on July 5. Blood: no path. evidence. Prothrombin index 53. Temp. about 37° C.

Autopsy. Skin cyanotic. Subpleural, subpericardial, and subarachnoidal asphyctic haemorrhages. No gross intracranial lesions. Lungs: light red, partially aerated. No deformities of the heart or vessels. Heart, especially the right ventricle, seemed to be dilated.

Electrocardiogram traced on afternoon July 5 (time not recorded): no definite auricular complexes distinguishable. Regular rhythm, frequency 80. Autonomic ventricular rhythm. QRS-complexes widened to 0.40; they may have contained a P-wave, in which case a partial atrioventricular block of Grade I with P—Q = 0.60 sec. was present.

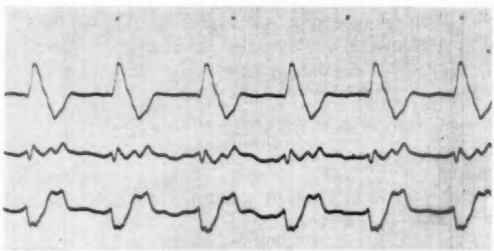

Fig. 1.

Summary of the electrocardiographic findings: bradycardia with markedly widened ventricular complexes, probably an autonomic ventricular rhythm (although atrioventricular block could not be definitely excluded).

Case 2. (1826/47.) Girl b. Oct. 5, 1947. Died the same day at 4.15 p.m. after living about fourteen and a half hours. Full-term delivery. Mother Para I. During partus mother developed fever, chills, and signs of cystitis. Foetal sounds normal. Spontaneous delivery. Infant profoundly asphyctic at birth. In spite of vigorous stimulating measures insufficient respiration; cyanosis persisted. Infant was therefore transferred to Children's Hospital at 9.15 a.m., where her condition persisted. Respiration at first feeble, shallow, ineffective, frequency 20—22 min. Heart: tachycardia, auscultated frequency about 200 per min. Tonus impaired. General, slightly greyish cyanosis. Throat clear at aspiration, defence reflexes present. Continuous inhalations of oxygen led to a certain improvement of condition: colour improved, breathing became somewhat more efficient, heart frequency 170 per min. At 12.15 p.m. cries of cerebral type interrupted by gasping, convulsive inspirations. At 2.40 p.m. sudden and rapid deterioration in condition. Respiration frequency now 25—30 min. Heart frequency also more irregular and slow; at about 2.30 p.m., 50/min. The breathing became more and more irregular. Died 4.15 p.m. At admittance fever was 39.9° C. and gradually falling; at death 36.2° C. Blood count normal. Had received K-vitamin injections at partus and later.

Autopsy. General cyanosis. Cerebral membranes and brain: no path. changes. Subserous asphyctic haemorrhages in the pleurae and pericard. Lungs: generally dark red except anterior portion of right lower lobe, which was light red and distinctly aerated, while the rest of the lung was firm. Here and there white matter from the small bronchial branches. Otherwise no gross abnormities. Microscopic examination of lungs revealed a discharge containing a moderate amount of meconium-like pigment

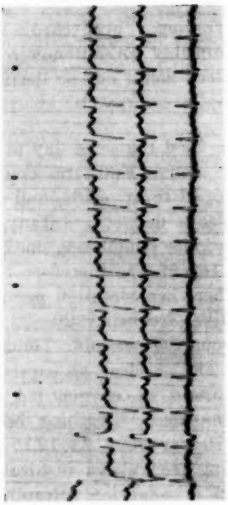

Fig. 2 a.

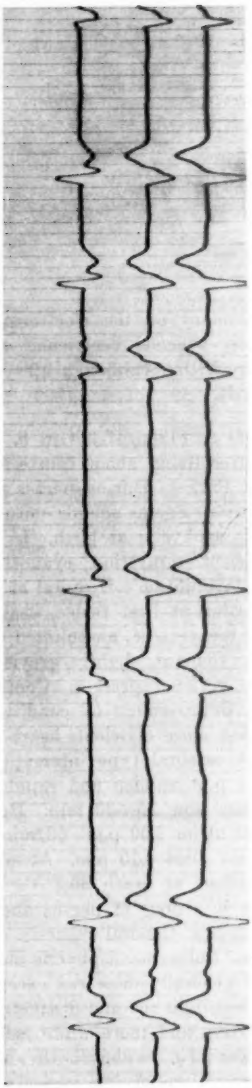

Fig. 2 b.

grains but on the other hand only a few squamous epithelial cells. About half of the alveoli seemed to be inflated and about half of these were aerated. In some of the bronchioli and in patches of the alveoli there was a thin exudate containing small quantities of fibrin and varying quantities of multinuclear leukocytes. Pronounced general hyperaemia. Thus this was a case of incipient bronchopneumonia.

Electrocardiogram:

1. 9.30 a.m. Regular sinus rhythm. Frequency 200. P—Q 0.13. QRS 0.08, normal. S—T normal. T_1—T_2 pos. T_3 neg. Normal ECG.
2. 2.30 p.m. No P-waves detectable. Irregular rhythm with very slow frequency. Markedly deformed QRS-complexes of ventricular extrasystolic type. The complexes were of two types and in groups of two—three.

Summary of electrocardiographic findings: after a normal ECG during initial stage of asphyxia a pronounced bradycardia with autonomic ventricular rhythm appeared about two hours before death.

Case 3. (2134/47.) Boy b. 8.30 a.m., died same day 5.15 p.m. Wt. 4 580 g. This child lived only about nine hours. Full-term delivery. Mother Para I. Spontaneous delivery without signs of asphyxia. Cyanosis and insufficient respiration at birth. In spite of vigorous stimulating measures and continuous inhalation of oxygen, asphyxia persisted stubbornly. Baby was therefore transferred to the Children's Hospital about three hours after partus. On admittance profound general cyanosis. Respiration regular, about 30/min., but shallow and not very efficient. Breathing was, however, still audible. Weak, wailing cries. Child lay still, limbs flaccid. Temp. 34.4° C. Heart sounds were somewhat muffled, frequency about 120/min.

Child's condition deteriorated considerably at about 2 p.m. He then lay flaccid and quite still and did not react to prickings of the skin. Cyanosis more intense but pale patches of skin between the cyanotic parts. Respiration still regular, about 30/min., but shallow. Heart frequency still about 120/min. In spite of application of warmth, temp. remained 34° C. Gradual deterioration in respiration, the pauses between every breath becoming longer; bradycardia. Died 5.15 p.m. Blood counts normal. Prothrombin index 54.

Autopsy. General cyanosis. Subperiostal extradural haemorrhages in the vertebral canal but without any compression effect. No fractures. Lungs: dark red with relatively small demarcated darker red patches of firm consistency. Sectional surface of lung was macroscopically rich in blood. Otherwise no abnormalities. Micr. examination of the lungs revealed that the alveoli were almost completely inflated and most of them contained oedematous fluid. Only a small portion, about 1/10, of the alveoli contained air. The oedematous fluid was blood-stained from ex-

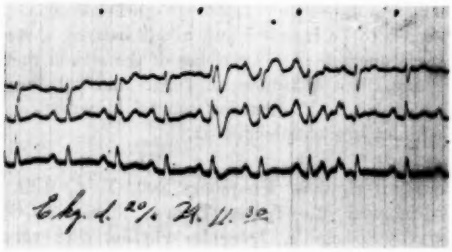

Fig. 3 a.

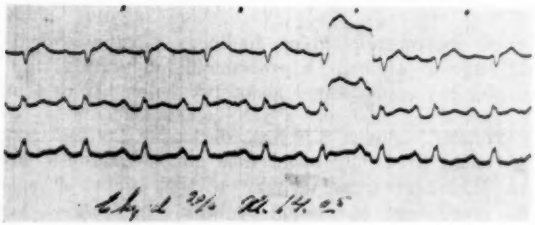

Fig. 3 b.

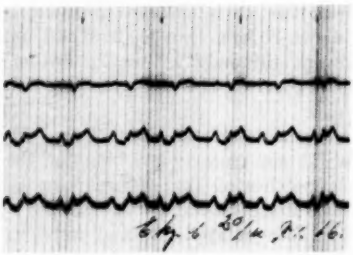

Fig. 3 c.

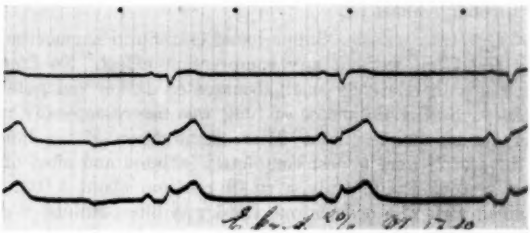

Fig. 3 d.

tensive haemorrhages in several places. A slight to moderate aspiration of some meconium pigment and in some places squamous epithelium was seen. Severe general hyperaemia. No signs of pneumonia.

Electrocardiogram:

1. 11.30 a.m. Regular sinus rhythm. Frequency 120. P—Q 0.18. QRS-complex 0.06. P_2 0.20. QRS-complex slightly deformed, S—T normal. T_1—T_2 pos., low, T_3 isoelectric.
2. 2.05 p.m. Regular sinus rhythm. Frequency 110. P—Q 0.21. QRS-complex 0.10. S—T_3 slightly depressed. T_1—T_2 pos. T_3 neg.
3. 4.55 p.m. Regular sinus rhythm. Frequency 110. S—T_{2-3} high. T_2—T_3 pos.
4. 5.10 p.m. Frequency 50. S—T_{2-3} elevation now still more marked. T_2—T_3 higher than before.

Summary of electrocardiographic findings: after a transient slight degression of the S—T_3 the ECG pattern changed to that of an acute posterior infarction.

Case 4. (975/48.) Boy b. 5 a.m. April 29. Died 6.40 p.m. same day (lived barely fourteen hours). Wt. 2 770 g. Delivery about six weeks earlier than expected after about six hours' labour. Mother Para II; first child, also premature, still alive. Infant showed no signs of asphyxia in utero or at birth. Normal respiration and cry. About six hours after partus sudden onset of cyanosis and insufficient respiration with cries. Infant transferred from nursing home to Children's Hospital. The whole time flaccid, cyanotic, with maer. shallow but regular respiration about 70/min. Heart sounds clear, initially of normal frequency, at auscultation about 135/min. Blood counts normal. Hypothrombinaemia in spite of prophylactic administration of K-vitamin at birth as well as at the onset of the asphyctic symptoms.

A gradual deterioration in respiration soon followed with gasping of low frequency, about 12/min. Heart frequency upon auscultation at commencement of the pronounced insufficient respiration about 110/min. However, bradycardia soon set in. Died about 45 min. after the commencement of the bradycardia.

Autopsy. Signs of haemorrhagic diathesis in the form of, among other things, small blood clots adherent to the choroid plexus in the lateral ventricles; also general asphyctic haemorrhages in the serous membranes, excessive hyperaemia with haemorrhages in the lungs. Signs of general stasis. No gross anatomic intracranial lesions in the form of dural or visible vascular ruptures. Microscopic examination of the lungs revealed that aspiration had taken place: in the alveoli abundant meconium bodies and meconium pigment with very few squamous epithelial cells were found. About three quarters of the alveoli were inflated and were lined throughout with vernix membranes. Most of these alveoli were

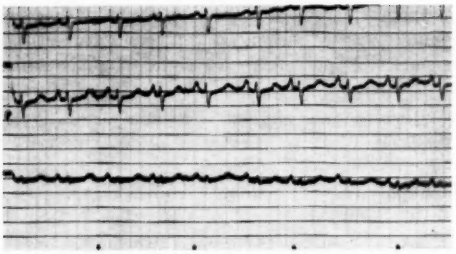

Fig. 4 a.

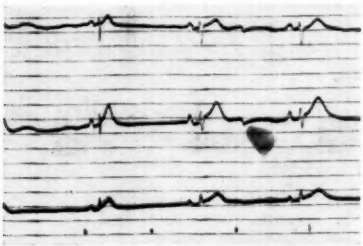

Fig. 4 b.

full of clear oedematous fluid. Pronounced general hyperaemia and extensive haemorrhages. No signs of pneumonia. Also other internal organs showed microscopic signs of general hyperaemia with small haemorrhages and general stasis.

Electrocardiogram:

1. 2.50 p.m. Regular sinus rhythm. Frequency 110. P—Q 0.12. QRS-complex 0.06. P_3 0.25. QRS: normal. S—T: nothing abnormal. T_1—T_2 pos.
2. 5.40 p.m. Regular sinus rhythm. Frequency 50. P—Q 0.15. QRS-complex 0.06. S—T_1 slightly elevated. S—T_{2-3} abnormal. T-waves high. T_1—T_3 higher than before.

Summary of the electrocardiographic findings: slowing of frequency. Deviation of QRST as in acute infarction.

Electrocardiographic examinations of three other fatal cases were also made. In two of these asphyxia was markedly intermittent throughout, pallor was absent, and respiration was satisfactory between attacks. Sudden death occurred in association

with a sudden attack of complete respiratory standstill. Electrocardiograms during the intervals were without substantial changes. The third case was likewise one of persistent but mainly intermittent asphyxia with relatively short attacks of insufficient respiration. The electrocardiograms were on the whole normal, apart from the one traced one hour before death and after a two hour attack of asphyxia. Here the electrocardiogram showed only somewhat decreased frequency (120 as compared with 150 before), nodulated and deformed QRS-complex, slight changes of S—T segment, and pos. T_1—T_3 higher than before. Electrocardiograms in some other cases of persistent asphyxia neonatorum where the infants survived exhibited only slight pathological features that disappeared with the abatement of the asphyxia.

For want of space no detailed account or reproduction of the electrocardiograms of the briefly described cases will be given.

Discussion

In all of the four cases reported in detail marked ECG changes occurred sub finem vitae in the course of a persistent asphyxia with insufficient respiration and cyanosis. It is obvious that the changes were solely or at least mainly due to anoxia.

The ECG changes were of two types. In two cases (3 & 4) they were of the type generally met with in cardiac infarction. In the other two cases the ECG showed changes rather characteristic of autonomic ventricular rhythm. Case 2 apparently had autonomic ventricular rhythm, while in Case 1 P-waves may have been present, but if so with a prolonged conduction time.

The ECG changes sub finem vitae described here were undoubtedly evidence of profound irreversible functional changes of the heart. This also applies to the very conspicuous bradycardia. The apparent changes observed in the patients also suggested the appearance of serious cardial insufficiency in connection with marked deterioration in the general condition of the patients.

The delay observed in the onset of bradycardia in prolonged asphyxia is of interest in the interpretation of bradycardia in

intrauterine asphyxia. This question will not be dealt with in this publication, however.

As pointed out above, no substantial ECG changes were observed in the cases of persistent asphyxia which recovered. This also applies to the fatal cases in which a relatively good general condition suddenly deteriorated and quickly ended in sudden death with total respiratory standstill. Here it was a question of an acute, severe anoxia rapidly leading to death. Therefore the previous condition of the heart probably played no role at all in the acute catastrophe.

Comments

Judging by a rapid perusal of the literature, the performance of electrocardiographic examinations in asphyxia neonatorum has not been reported. On the other hand, however, a number of clinical publications are available on electrocardiographic tracings made shortly before the deaths of patients of other ages, generally adults, which might be relevant.

STROUD & FEIL (1948) have reported twenty three cases of their own of this type and also given a review of earlier publications. Of greatest interest for the elucidation of my observations reported above are the cases which they deal with under the heading *Slow Death* (»Anoxic and Hemorrhagic Shock»). Summarizing, they say among other things, »... The course of events is sinus slowing, nodal rhythm, ectopic ventricular systoles, ventricular rhythm, slowing and stoppage. Ventricular fibrillation occurs usually when there is ventricular tachycardia and ectopic ventricular beats or following a period of asystole.»

HARRIS has shown in experiments on dogs that the course of events in prolonged anoxaemia (or haemorrhage) is analogous.

In the two cases (1 & 2) in which an autonomic ventricular rhythm was probably or definitely diagnosed, the electrocardiographic findings were compatible with the observations made by HARRIS and STROUD & FEIL, whereas the electrocardiographic pattern reminiscent of cardiac infarction found in my Cases 3 and 4 has not, as far as I can see, been observed by these authors (apart, of course, from the ECG in clinical or experimental cases

of coronary occlusion). This difference is perhaps attributable to the fact that all the electrocardiograms published here were preagonal (with the possible exception of ECG 4, Case 3) while both STROUD & FEIL and HARRIS paid most attention to the agonal electrocardiogram. Of interest is the general slowing of the cardial activity throughout the whole of their material. It is apparently characteristic of anoxic diseases of the heart and was also present in my cases.

In his animal experiments HARRIS was able to show that sectioning of the vagus nerves prevents the initial slowing. STROUD & FEIL therefore assert that in anoxaemic emergencies where the individual is otherwise in good general condition the vagal implication suggests that the use of atropine might prevent cardiac standstill. Perhaps the therapeutic administration of atropine or similar substances may be indicated in the initial stage of such asphyxia neonatorum as shows a tendency to be persistent.

Summary

Some electrocardiographic examinations of newborn infants suffering from prolonged asphyxia are described.

1. In asphyctic cases with a favourable course only slight or insignificant electrocardiographic abnormalities were present.

2. In those cases in which sudden death occurred during an acute asphyctic attack, the electrocardiogram was on the whole normal or only slightly abnormal before the catastrophic issue.

3. The electrocardiogram taken shortly before death in fatal cases of persistent asphyxia showed two types of changes: (a) autonomic ventricular rhythm, and (b) changes similar to coronary occlusion. Bradycardia was marked in both types. The changes were interpreted as signs of a general, profound, anoxic lesion of the heart.

In conclusion, I should like to thank Bo Ewert, M.D., for his valuable assistance with the description and interpretation of the electrocardiograms.

Résumé

Electrocardiographie dans des cas d'asphyxie prolongée chez des nouveau-nés

Description est faite de quelque examens électrocardiographiques de nouveau-nés atteints d'asphyxie prolongée.

1. Dans le cas d'asphyxie avec développement favorable, on ne relève que des anormalités électrocardiographiques légères ou insignifiantes.

2. Dans ceux où la mort eut subitement lieu au cours d'une crise aiguë d'asphyxie, l'électrocardiogramme fut dans l'ensemble normal ou simplement anormal avant le dénouement fatal.

3. L'électrocardiogramme pris un moment avant la fin dans un cas mortel d'asphyxie persistante montre deux types d'altérations: (a) le rythme ventriculaire autonome et (b) des altérations similaires à celles de l'occlusion coronaire.

Une bradicardie fut notée dans les deux cas. Les altérations furent interprétées comme signes de lésion du coeur générale, profonde et anoxique.

Zusammenfassung

Elektrokardiographie bei anhaltender Asphyxie bei Neugeborenen

Es wurden einige elektrographische Untersuchungen bei Neugeborenen mit anhaltender Asphyxie beschrieben.

1. Bei Fällen von Asphyxie mit günstigem Verlauf waren nur leichte oder unbedeutende elektrokardiographische Abnormalitäten vorhanden.

2. In Fällen, wo Mors subita während eines akuten Anfalles von Asphyxie eintrat, war das Elektrokardiogramm im allgemeinen normal oder ganz wenig abnormal vor dem tötlichen Ausgang.

3. Das Elektrokardiogramm, das in einigen Fällen hartnäckiger Asphyxia kurz vor Eintritt des Todes aufgenommen wurde, zeigte zwei Typen von Veränderungen und zwar a) einen autonomen Rhythmus in der Herzkammer, b) Veränderungen ähnlich dem Verschluss der Kranzadern.

Bradykardie war in beiden Typen merkbar. Die Veränderungen wurden als Zeichen einer allgemeinen, tiefgehenden, anoxischen Veränderung des Herzens angesehen.

Sumario

Electrocardiografía en la asfixia prolongada del recién nacido

Se describen algunos examenes electrocardiográficos en recién nacidos con asfixia prolongada.

1) En los casos de asfixia a evolución favorable, solamente se constataron pequeñas anormalidades insignificantes en el electrocardiograma.

2) En los casos de muerte súbita ocurrida en el curso de un acceso de asfixia aguda, el electrocardiograma era completamente normal, o solo ligeramente anormal antes del fin catastrofico.

3) El electrocardiograma tomado un poco antes de la muerte, en los casos fatales de asfixia persistente mostraron 2 tipos de alteraciones a) ritmo autónomo ventricular y b) cambios similares a la aclución coronaria. Marcada bradicardia en ambos tipos. Las alteraciones fueron interpretadas como una lesión anoxica generalizada y profunda del corazón.

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HARRIS, A .S.: Ibid. *35:* 895, 1948.

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